08/702114

PTO/SB/17 (10-08)
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Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2009

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 1,120.00

Complete if Known	
Application Number	08/702,114 (Patent No. 5,861,379)
Filing Date	Aug 23, 1996 (Issued: Jan 19, 1999)
First Named Inventor	Michael Ibea
Examiner Name	Anish Gupta
Art Unit	1654
Attorney Docket No.	16575.0002USI2

RECEIVED
DEC 15 2010
PATENT EXTENSION
OPLA

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☑ Deposit Account Deposit Account Number: 13-2725 Deposit Account Name: Merchant & Gould

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☑ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☑ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17 ☑ Credit any overpayments

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

Application Type	FILING FEES Fee ($)	FILING FEES Small Entity Fee ($)	SEARCH FEES Fee ($)	SEARCH FEES Small Entity Fee ($)	EXAMINATION FEES Fee ($)	EXAMINATION FEES Small Entity Fee ($)	Fees Paid ($)
Utility	330	165	540	270	220	110	
Design	220	110	100	50	140	70	
Plant	220	110	330	165	170	85	
Reissue	330	165	540	270	650	325	
Provisional	220	110	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	52	26
Each independent claim over 3 (including Reissues)	220	110
Multiple dependent claims	390	195

Total Claims	Extra Claims	Fee ($)	Fee Paid ($)
_____ - 20 or HP =	_____ x	_____ =	_____

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims	Extra Claims	Fee ($)	Fee Paid ($)
_____ - 3 or HP =	_____ x	_____ =	_____

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims Fee ($)	Multiple Dependent Claims Fee Paid ($)
_____	_____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $270 ($135 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
_____ - 100 =	_____ / 50 =	_____ (round up to a whole number) x	_____ =	_____

4. OTHER FEE(S)

Non-English Specification, $130 fee (no small entity discount) Fees Paid ($)

02/08/2011 RLOGAN 00000001 13275 08702114
01 FC:1457 1120.00 DA 1,120

Other (e.g., late filing surcharge): Request for Extension of Patent Term Under 35 USC 156

SUBMITTED BY					
Signature	Dianna Goldenson	Registration No. (Attorney/Agent)	52,949	Telephone	646-783-4294
Name (Print/Type)	Dianna Goldenson			Date	December 15, 2010

U.S. Patent No. 5,861,379 Attorney Docket No.: 16575.0002USI2

Certificate of Express Mailing Under 37 CFR 1.10

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail, Airbill No. EG 681168230US in an envelope addressed to:

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

on December 15, 2010
Date

Signature

Randall Douglas
Typed or printed name of person signing Certificate

Registration Number, if applicable

646-783-4296
Telephone Number

Note: Each paper must have its own certificate of mailing, or this certificate must identify each submitted paper.

Request for Extension of Patent Term Under 35 U.S.C. §156 (13 pp. x 5 copies) Exhibits A-L (x 5 copies)
Exhibit A (3 pp.); Exhibit B (2 pp.); Exhibit C (56 pp.); Exhibit D (18 p p.); Exhibit E (2 pp.); Exhibit F (1 p.); Exhibit G (3 pp.); Exhibit H (2 pp.); Exhibit I (3 pp.); Exhibit J (6 pp.); Exhibit K (12 pp.); Exhibit L (3 pp.)
Fee Transmittal Form (1 p.)
Charge $1,120.00 to Deposit Account Number 13-2725
Return Receipt Postcard (1 p.)

Customer No.: 23552 Docket No.: 16575.0002USI2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 5,861,379

Inventors: Michel Ibea, Thierry Abribat, and Paul Brazeau

Assignee: Theratechnologies Inc.

Title: CHIMERIC FATTY BODY-PRO-GRF ANALOGS WITH INCREASED BIOLOGICAL POTENCY

Issue Date: January 19, 1999

REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Mail Stop Hatch-Waxman PTE
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Theratechnologies Inc., the owner of U.S. Patent No. 5,861,379 ("the '379 patent"), hereby requests an extension of the term of the '379 patent pursuant to 35 U.S.C. §156. The assignment of the '379 patent from the inventors to Theratechnologies Inc. is recorded at reel 8227, frame 0671 (recorded on August 23, 1996). A copy of the recorded assignment is attached as Exhibit A. A Power of Attorney executed by an officer of Theratechnologies Inc. is attached as Exhibit B.

A total of five copies of this application are submitted in compliance with 37 C.F.R. §1.740(b) and as suggested by MPEP §2753.

The following information is submitted in accordance with 35 U.S.C. §156(d) and 37 C.F.R. §1.740, and follows the numerical format set forth in 37 C.F.R. §1.740(a):

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.

The approved product will be marketed under the trademark EGRIFTA™ for administration by subcutaneous injection. The active ingredient of EGRIFTA™ has

(a) the chemical names of

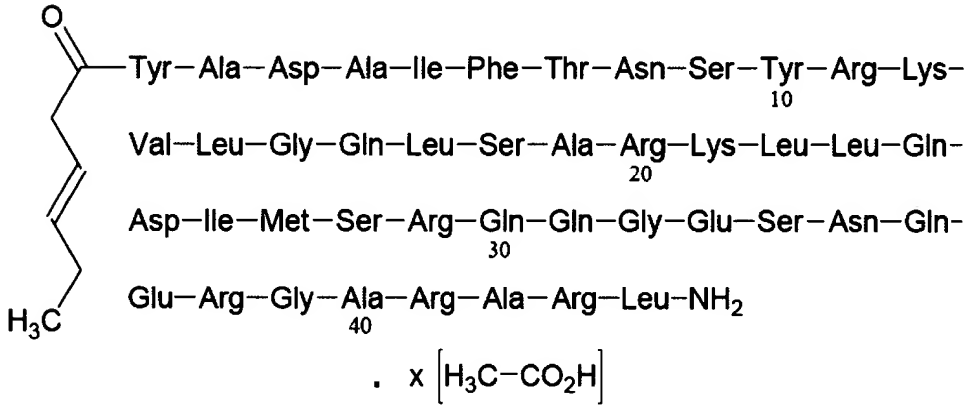
1. L-Leucinamide, N-[(3E)-1-oxo-3-hexenyl]-L-tyrosyl-L-alanyl-L-α-aspartyl-L- alanyl-L-isoleucyl-L-phenylalanyl-L-threonyl-L-asparaginyl-L-seryl-L-tyrosyl-L- arginyl-L-lysyl-L-valyl-L-leucylglycyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L- arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-α-aspartyl-L-isoleucyl-L- methionyl-L-seryl-L-arginyl-L-glutaminyl-L-glutaminylglycyl-L-α-glutamyl-L- seryl-L-asparaginyl-L-glutaminyl-L-α-glutamyl-L-arginylglycyl-L-alanyl-L-arginyl-L-alanyl-L-arginyl-, acetate (salt);

2. (3E)-hex-3-enoylsomatoliberin (human) acetate (salt); and

3. N-(*trans*-3-Hexenoyl)-Human Growth Hormone Releasing Factor (1-44) Acetate

(b) the generic name of Tesamorelin Acetate (also referred to as TH9507);

(c) the structural formula of:



(d) the empirical formula of $C_{221}H_{366}N_{72}O_{67}S \bullet x\ C_2H_4O_2$; and

(e) the molecular weight of tesamorelin as a free base of 5135.9 Da (i.e., without acetates).

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.

The regulatory review occurred under §505(b) of the Federal Food, Drug and Cosmetic Act (FFDCA), which is codified at 21 U.S.C. §355(b). Section 505(b) (21 U.S.C. §355(b)) provides for the submission and approval of New Drug Applications (NDAs).

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.

EGRIFTA™ (tesamorelin for injection) received permission for commercial marketing from the Food and Drug Administration (FDA) pursuant to §505(b) of the FFDCA (21 U.S.C. §355(b)) on November 10, 2010. A copy of the letter from the FDA approving the marketing of EGRIFTA™ (tesamorelin for injection) is attached as Exhibit C.

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

The active ingredient in the approved product is tesamorelin. Tesamorelin was not previously approved for commercial marketing or use under the FFDCA, the Public Health Service Act, or the Virus-Serum-Toxin Act prior to the approval referenced herein on November 10, 2010.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the date of the last day on which the application could be submitted.

EGRIFTA™ (tesamorelin for injection) was approved for commercial marketing on November 10, 2010. The sixty day period expires on January 8, 2011. The present application, therefore, is timely filed within the sixty day period.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.

Inventors: Michel Ibea, Thierry Abribat, and Paul Brazeau

Patent No.: US 5,861,379

Issue Date: January 19, 1999

Expiration Date: May 26, 2015

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.

A copy of the '379 patent is attached as Exhibit D.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.

During prosecution of the '379 patent, a terminal disclaimer was filed over U.S. Patent Application No. 08/702,113 (now U.S. Patent No. 5,939,386). A copy of the terminal disclaimer filed for the '379 patent is attached as Exhibit E.

A certificate of correction was issued for the '379 patent on July 6, 2010. A copy of the certificate of correction is attached as Exhibit F.

The 3½ year, 7½ year, and 11½ year maintenance fees for the '379 patent have been timely paid. Copies of the receipts showing payment of the 3½ year, 7½ year, and 11½ year maintenance fees are attached as Exhibit G.

No reexamination certificates have been issued for the '379 patent.

(9) A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on:

(i) **The approved product, if the listed claims include any claim to the approved product;**

(ii) **The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and**

(iii) **The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product.**

The approved product, EGRIFTA™ (tesamorelin for injection), is administered in the form of an injectable solution in which tesamorelin is in the presence of acetate counterions. The acetate counterions are used to stabilize the peptide portion of tesamorelin and provide no therapeutic effect. Thus, tesamorelin is the active ingredient in EGRIFTA™ (tesamorelin for injection) that is therapeutically active when administered to a patient.

Claims 1-5 and 7-9 in the '379 patent cover tesamorelin, or a pharmaceutical formulation comprising tesamorelin, and thus read on the approved product. *See* MPEP §2751 (stating that "a 'product' is a 'drug product,'" a "'drug product' means the active ingredient found in the final dosage form prior to administration of the product to the patient," and an "active ingredient of a drug is the ingredient in the drug product that becomes therapeutically active when administered").

The structural formula of tesamorelin is:

transCH_3—CH_2—CH=CH—CH_2—CO-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu-NH_2.

Claim 8 is explicitly directed to tesamorelin and calls for a chimeric fatty body GRF analog having the formula:

transCH_3—CH_2—CH=CH—CH_2—CO-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu-NH_2.

Other claims in the '379 patent that read on the approved product include claims 1-5, 7, and 9. For instance, claim 1 reads on tesamorelin when, in the claimed general formula, A1 is Tyr; A2 is Ala; A8 is Asn; A18 is Ser; A15 is Gly; A24 is Gln; A27 is Met; A28 is Ser; A30 is Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu; R_0 is NH_2; and A1 is N-

anchored by a hydrophobic tail of general formula I wherein G is a carbonyl group; a is 1; b is 0; c is 0; d is 0; e is 1; R_2 is hydrogen; f is 1; W'=Y' is trans (CH=CR_6); R_6 is hydrogen; g is 2; R_3 is hydrogen; R_4 is hydrogen; and h is 0; wherein the sum of d+f = 1 and the sum of a, b, c, d, e, f, g and h is such that the hydrophobic tail of formula I has a linear main chain of 6 carbon atoms. Claims 2-5 and 7 also read on tesamorelin. Additionally, claim 9 reads on a pharmaceutical formulation comprising tesamorelin, and claims 10 and 17 read on methods of using tesamorelin.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product:

(A) The effective date of the investigational new drug (IND) application and the IND number;

(B) The date on which a new drug application (NDA) application or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and

(C) The date on which the NDA was approved or the Product License issued;

(ii) For a patent claiming a new animal drug ...

(iii) For a patent claiming a veterinary biological product ...

(iv) For a patent claiming a food or color additive ...

(v) For a patent claiming a medical device ...

The investigational new drug (IND) application for EGRIFTA™ (tesamorelin for injection) is IND Application No. 61,226. Theratechnologies Inc. filed the IND application on October 15, 2001 (Exhibit H). The IND became effective on November 15, 2001 – i.e., the exemption under 21 U.S.C. §355(i) became effective 30 days after receipt of the IND application by the FDA pursuant to 21 U.S.C. §355(i)(2). A copy of the letter from the FDA acknowledging receipt of the IND for EGRIFTA™ (tesamorelin for injection) is attached as Exhibit I.

The NDA for EGRIFTA™, NDA No. 22-505, was initially submitted to the FDA on May 29, 2009 (Exhibit J).

NDA No. 22-505 was approved by the FDA on November 10, 2010 (a copy of the FDA letter approving marketing is attached as Exhibit C).

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

Theratechnologies Inc., the owner of the '379 patent, submitted an IND application for tesamorelin on October 15, 2001 (Exhibit H). In a letter dated October 24, 2001, the FDA acknowledged receipt of the IND application on October 16, 2001 and assigned it IND No. 61,226 (Exhibit I). According to 21 U.S.C. §355(i)(2), clinical investigation of a drug may begin 30 days after receipt of the IND application by the FDA. Thus, the IND became effective on November 15, 2001 (Exhibit I), after which Theratechnologies Inc. promptly began its U.S. investigation of EGRIFTA™ (tesamorelin for injection) – e.g., by initiating a Phase II study. A chronology of the U.S. regulatory review of EGRIFTA™ (tesamorelin for injection) (also referred to as TH9507) is attached as Exhibit K.

After the studies referenced in the IND were initiated, the FDA was kept apprised of protocol amendments, new investigator information, annual reports, press releases, safety reports, and other information and activities related to the regulatory review of EGRIFTA™ (tesamorelin for injection). Meetings, including teleconferences, with the FDA and Theratechnologies Inc. were also conducted in relation to the IND activities in an effort to diligently advance the regulatory review.

On May 29, 2009, Theratechnologies Inc. submitted an NDA for EGRIFTA™, which was assigned number 22-505 (Exhibit J). The FDA acknowledged receipt of NDA No. 22-505 in a letter dated June 17, 2009 (Exhibit L). Theratechnologies Inc. promptly complied with all FDA requests for information during the NDA review (*see, e.g.*, the list of submissions to the FDA acknowledged in the FDA approval letter for EGRIFTA™ (tesamorelin for injection) attached as Exhibit C). The NDA was approved on November 10, 2010.

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of the extension was determined.

It is the opinion of the applicant that the '379 patent is eligible for patent term extension under 35 U.S.C. §156(a). The applicant claims an extension of 1827 days.

Statement of Eligibility of the Patent for Extension Under 35 U.S.C. §156(a)

Section 156(a) provides in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted; (2) the term of the patent has never been extended under 35 U.S.C. §156(e)(1); (3) the application for extension is submitted by the owner of record of the patent or its agent and in accordance with 35 U.S.C. §156(d); (4) the product has been subject to a regulatory review period before its commercial marketing or use; and (5) except for 35 U.S.C. §§156(a)(5)(B) and 156(a)(5)(C), the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

Each of these elements is satisfied here:

(1) The term of the '379 patent expires on May 26, 2015. This application has, therefore, been submitted before the expiration of the patent term.

(2) The term of the '379 patent has never been extended.

(3) The application is submitted by Dianna Goldenson, an attorney for the patent owner, Theratechnologies Inc. This application is submitted in accordance with 35 U.S.C. §156(d) in that it is submitted within the sixty day period beginning November 10, 2010 when the product received permission for marketing under the FFDCA and contains the information required under 35 U.S.C. §§156(d)(1)(A)-(E).

(4) The product was the subject of an IND (filed on October 15, 2001 and effective on November 15, 2001), and an NDA (filed on May 29, 2009 and approved on November 10, 2010). Thus, the product was subject to a regulatory review period under §505(b) of the FFDCA before its commercial marketing or use.

(5) The permission for the commercial marketing of EGRIFTA™ (tesamorelin for injection) after regulatory review under FFDCA §505(b) is the first permitted commercial marketing of tesamorelin in the United States. This is confirmed by the absence of any approved NDA under which tesamorelin could be commercially marketed prior to November 10, 2010.

Statement as to the Length of the Extension Claimed In Accordance with 37 C.F.R. §1.775

The term of the '379 patent should be extended by 1827 days. The extension was determined according to 37 C.F.R. §1.775 as follows:

(1)	2753	The number of days in: the period beginning on the effective date of the IND (November 15, 2001) and ending on the date the NDA was initially submitted (May 29, 2009). This is the "testing phase" as defined in 37 C.F.R. §1.775(c)(1).
(2)	531	The number of days in the period beginning on the date the NDA was initially submitted (May 29, 2009) and ending on the date of NDA approval (November 10, 2010). This is the "approval phase" as defined in 37 C.F.R. §1.775(c)(2).
(3)	3284	The sum of (1) and (2). This is the regulatory review period as define in 37 C.F.R. §1.775(c).
(4)	0	The number of days in the approval phase (2) which were on and before issuance of the '379 patent. 37 C.F.R. §1.775(d)(1)(i).
(5)	0	The number of days in the approval phase (2) during which the Applicant did not act with due diligence. 37 C.F.R. §1.775(d)(1)(ii).
(6)	0	The sum of (4) and (5).
(7)	3284	The difference between the regulatory review period (3) and (6). 37 C.F.R. §1.775(d)(1)(ii).
(8)	0	The number of days of the period of the testing phase (1) which occurred prior to the issuance of the '379 patent. 37 C.F.R. §1.775(d)(1)(i).
(9)	0	The number of days of the period of the testing phase (1) during which the Applicant failed to act with due diligence 37 C.F.R. §1.775(d)(1)(ii).
(10)	0	The sum of (8) and (9).
(11)	3284	The difference between the regulatory review period (7) and (10).
(12)	2753	The number of days of the testing phase (1).
(13)	0	The number of days from (10).
(14)	2753	Subtract line (13) from line (12)
(15)	1376	One half of (14) 37 C.F.R. §1.775(d)(1)(iii)[1]
(16)	1908	Subtract line (15) from line (11)
(17)	May 26, 2015	The original expiration date of the '379 patent.
(18)	Aug. 15, 2020	The expiration date of the '379 patent if the original expiration date is

[1] 37 C.F.R. §1.775(d)(1) provides that for purposes of subtraction, half days are ignored.

		extended by the number of days in line (16). 37 C.F.R. §1.775(d)(2)
(19)	Nov. 10, 2010	The date of approval of the application under §505(b) of the FFDCA.
(20)	14 years	The limitation of 37 C.F.R. §1.775(d)(3).
(21)	Nov. 10, 2024	The number of years in (20) plus the date on (19). 37 C.F.R. §1.775(d)(3).
(22)	Aug. 15, 2020	The earlier of line (18) or line (21)
(23)	May 26, 2015	The original expiration date of the '379 patent.
(24)	5 years	The applicable limitation of 37 C.F.R. §1.775(d)(5)
(25)	May 26, 2020	The number of years on (24) plus the date on (23).
(26)	May 26, 2020	The earlier of line (22) or line 25
(27)	May 26, 2015	The original expiration date of the '379 patent
(28)	1827 days	The number of days which is the difference between the date on line (27) and the date on line 26

(13) A statement that applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought for the '379 patent by this Request as required by 37 C.F.R. §1.765.

(14) The prescribed fee for receiving and acting upon the application for extension.

Payment in the amount of $1,120 as required under 37 C.F.R. §1.20(j) is submitted with this Request. The Commissioner is hereby authorized and requested to charge any deficiency owed and/or credit any refund due to Deposit Account No. 13-2725.

(15) The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed

Dianna Goldenson, Esq.
Merchant & Gould P.C.
3200 IDS Center
80 South 8th Street
Minneapolis, MN 55402-2215
Tel: (646) 783-4294
Fax: (612) 332-9081

In view of the foregoing, patent owner Theratechnologies Inc. hereby requests that the Commissioner grant an extension of 1827 days to U.S. Patent No. 5,861,379.

Favorable action is earnestly solicited.

Dated: December 15, 2010

Respectfully submitted,

By Dianna Goldenson

Dianna Goldenson
Registration No.: 52,949
MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, MN 55402-0903
Phone: (646) 783-4294
Fax: (612) 332-9081
Attorney For Applicant

LIST OF EXHIBITS

Exhibit A	Assignment of the '379 patent from the inventors to Theratechnologies Inc. (recorded Aug. 23, 1996)
Exhibit B	Power of Attorney
Exhibit C	FDA approval letter for EGRIFTA™ (tesamorelin for injection) (Nov. 10, 2010)
Exhibit D	U.S. Patent No. 5,861,379 ("the '379 patent")
Exhibit E	Terminal disclaimer over U.S. Patent No. 5,939,386
Exhibit F	Certificate of Correction (July 6, 2010)
Exhibit G	Receipts for the 3½ year, 7½ year, and 11½ year maintenance fees
Exhibit H	Cover letter of IND Application No. 61,226 submitted to FDA (Oct. 15, 2001)
Exhibit I	Letter from FDA acknowledging receipt of IND application (Oct. 24, 2001)
Exhibit J	Cover letter of NDA submitted to FDA (May 29, 2009)
Exhibit K	Chronology of regulatory review of EGRIFTA™ (tesamorelin for injection)
Exhibit L	Letter from FDA acknowledging receipt of NDA (Jun. 17, 2009)

1912 ... A

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

JANUARY 22, 1997

PTAS

BIRCH, STEWART, KOLASCH & BIRCH, LLP
GERALD M. MURPHY, JR.
P.O. BOX 747
FALLS CHURCH, VA 22040-0747

100308453A

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, NORTH TOWER BUILDING, SUITE 10C35, WASHINGTON, D.C. 20231.

RECORDATION DATE: 08/23/1996

REEL/FRAME: 8227/0671
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BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
IBEA, MICHEL

DOC DATE: 08/15/1996

ASSIGNOR:
ABRIBAT, THIERRY

DOC DATE: 08/15/1996

ASSIGNOR:
BRAZEAU, PAUL

DOC DATE: 08/15/1996

ASSIGNEE:
THERATECHNOLOGIES INC.
7701, 17E AVENUE, MONTREAL
QUEBEC, CANADA H2A2S5

SERIAL NUMBER: 08702114
PATENT NUMBER:

FILING DATE: 08/23/1996
ISSUE DATE:

SHIRLIE SIMON, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

1912-151CIP

08/702114

ASSIGNMENT OF INVENTION
UNIVERSAL

WHEREAS, I/We Paul BRAZEAU; Thierry ABRIBAT; and Michel IBEA, have invented certain improvements in CHIMERIC FATTY BODY-GRF ANALOGS WITH INCREASED BIOLOGICAL POTENCY and described in a patent application executed on August 15, 1996 and:

WHEREAS, THÉRATECHNOLOGIES INC., 7701, 17e Avenue, Montréal, Québec, Canada H2A 2S5 (hereinafter referred to as the Assignee), is desirous of acquiring the entire right, title and interest in and to said invention or inventions and in and to any and all patents to be obtained therefore;

NOW, THEREFORE, in consideration of One Dollar ($1.00) and other valuable consideration, the receipt of which is hereby acknowledged, I/We have and by these presents do hereby sell, assign and transfer unto said Assignee, its successors and assigns, the entire right, title and interest in and to said invention or inventions, as described in the aforesaid application, in any form or embodiment thereof, and in and to the aforesaid application; and in and to any applications filed in any foreign country based thereon, including the right to file said foreign applications under the provisions of the International Convention; also the entire right, title and interest in and to any and all patents, reissues or extensions thereof to be obtained in this or any foreign country upon said invention or inventions, and any divisional, continuation, continuation-in-part, substitute application(s) or supplementary disclosure(s) which may be filed upon said invention or inventions, in any country; and I/We hereby authorize and request the issuing authority to issue any and all patents on said application or applications to said Assignee.

I/We further agree, without any payment by said Assignee other than expenses incurred by the undersigned, to communicate to said Assignee, its representatives or agents, any facts relating to said invention or inventions, including evidence for interference purposes or for other proceedings, whenever requested; testify in any interference, litigation or other proceedings, whenever requested; and execute and deliver, on request, all lawful papers required to make any of the foregoing provisions effective, and likewise make these provisions binding upon my/our heirs, legal representatives, administrators and assigns.

Le(s) soussigné(s) désire(nt) que la présente cession soit en anglais. The undersigned request(s) that the present assignment be in English.

IN WITNESS WHEREOF, I/We have hereunto set my/our hand(s) and seal this 15th day of August 1996.

Witness

Michel IBEA

Thierry ABRIBAT

Paul BRAZEAU

B

PTO/SB/81A (12-08)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT - POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Patent Number	5,861,379
Issue Date	January 19, 1999
First Named Inventor	Michel Ibea
Title	Chimeric Fatty Body-Pro-GRF Analogs With Increased Biological Potency
Attorney Docket Number	16575.0002USI2

I hereby revoke all previous powers of attorney given in the above-identified patent.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith: 23552

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified patent to:

☒ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☐ Inventor, having ownership of the patent.

OR

☒ Patent owner.

Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____.

SIGNATURE of Inventor or Patent Owner

Signature	France Leclaire	Date	Dec. 2, 2010
Name	France Leclaire	Telephone	(514) 336-7800
Title and Company	Assistant Director, Intellectual Property Management for Theratechnologies, Inc.		

NOTE: Signatures of all the inventors or patent owners of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Theratechnologies Inc.

Application No./Patent No.: U.S. Patent No. 5,861,379 Filed/Issue Date: Issued January 19, 1999

Titled: CHIMERIC FATTY BODY-PRO-GRF ANALOGS WITH INCREASED BIOLOGICAL POTENCY

Theratechnologies Inc., a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. [X] the assignee of the entire right, title, and interest in;

2. [ ] an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. [ ] the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. [X] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 008227, Frame 0671, or for which a copy therefore is attached.

OR

B. [ ] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet(s).

[ ] As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

France Leclaire
Signature

June 3, 2010
Date

France Leclaire
Printed or Typed Name

Ass. Dir., IP Management
Title

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022505

NDA APPROVAL

Kendle International, Inc.
Attention: Michelle Wilson, Ph.D.
Senior Regulatory Consultant
U.S. Agent for Theratechnologies, Inc.
44 Vine Street, Suite 500
Cincinnati, OH 45202

Dear Dr. Wilson:

Please refer to your New Drug Application (NDA) dated May 29, 2009, received May 29, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Egrifta (tesamorelin for injection), 1 mg/vial.

We acknowledge receipt of your amendments dated June 17 (2), 29, and 30, July 31, September 9 and 29, October 12, 29, and 30, November 20 and 30, and December 8, 17, 22, 24, and 28, 2009, and January 20 and 28, March 23, April 1, May 3, 12, and 17, June 2, 14, and 23, July 23, August 2 and 11, September 13, October 29, and November 10, 2010.

This new drug application provides for the use of Egrifta (tesamorelin for injection) for the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert and text for the patient package insert and patient instructions for use submitted on November 10, 2010). Information on submitting SPL files using eLIST may be found in the guidance for industry titled *SPL Standard for Content of Labeling Technical Qs and As* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate-container labels submitted on November 10, 2010, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22505.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because there is evidence strongly suggesting that the drug product would be unsafe in all pediatric age groups. Administering this drug to a patient population that has not yet completed growth may result in adverse events associated with supraphysiologic levels of growth hormone, including excessive linear growth.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk when available data indicate the potential for a serious risk of microbial contamination possibly resulting in soft tissue infections which can occur during product reconstitution; or identify an unexpected serious risk when available data indicate the potential for a serious risk of malignancies or diabetic retinopathy related to elevated IGF-1 levels; or assess signals of serious risks of glucose intolerance/diabetes mellitus and hypersensitivity reactions suggested by clinical trial data.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1708-1 Manufacturing studies to determine a process for providing a daily dose (2 mg) of lyophilized product in a single vial. This single vial would replace the container-closure system described in the original application in which the daily dose is provided in two separate vials each containing 1.1 mg of lyophilized powder.

The timetable you submitted on November 10, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	May 2011
Study Completion:	July 2012
Final Report Submission:	September 2013

1708-2 A long-term observational safety study of at least 10 years duration comparing patients with HIV-associated lipodystrophy and excess abdominal fat treated with Egrifta compared to a similar group of patients not treated with Egrifta to assess potential safety concerns associated with long-term administration of Egrifta, including but not limited to the occurrence of glucose intolerance/diabetes mellitus, hypersensitivity reactions, malignancies, liver abnormalities, kidney abnormalities, diabetic retinopathy, and major adverse cardiovascular events.

The timetable you submitted on November 10, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	May 2011
Study Completion Date:	December 2024
Final Report Submission:	August 2025

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify the unexpected serious potential risk of diabetic retinopathy and secondarily the unexpected serious potential risk of long-term effects of Egrifta on glucose metabolism and major adverse cardiovascular events (MACE).

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

1708-3 A prospective, randomized, placebo-controlled clinical trial to evaluate if Egrifta increases the risk of development or progression of diabetic retinopathy when administered to HIV-infected patients with lipodystrophy and concomitant

diabetes. The primary objective is to compare the percentage of subjects with a 3-step or greater progression in the Early Treatment Diabetic Retinopathy Study (ETDRS) scale after a minimum of three years of treatment with Egrifta versus placebo. The trial will also evaluate the long-term effect of Egrifta on glucose metabolism and conduct blinded adjudication for major adverse cardiovascular events (MACE).

The timetable you submitted on November 10, 2010, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	April 2011
Study Completion Date:	May 2016
Final Report Submission:	November 2016

Submit the protocols to your IND 061226, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)".**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Jennifer Johnson, Regulatory Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
Physician Labeling
Patient Labeling
Instructions for Use
Carton and Container Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **EGRIFTA™** safely and effectively. See full prescribing information for **EGRIFTA™**.

EGRIFTA™ (tesamorelin for injection) for subcutaneous use
Initial U.S. Approval: 2010

INDICATIONS AND USAGE

EGRIFTA™ is a growth hormone releasing factor (GRF) analog indicated for the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy. (1)

Limitations of use (1):

- Long-term cardiovascular benefit and safety of EGRIFTA™ have not been studied.
- Not indicated for weight loss management (weight neutral effect).
- There are no data to support improved compliance with anti-retroviral therapies in HIV-positive patients taking EGRIFTA™.

DOSAGE AND ADMINISTRATION

- Recommended dose of EGRIFTA™ is 2 mg injected subcutaneously once daily. (2.1)

DOSAGE FORMS AND STRENGTHS

- Each vial of EGRIFTA™ contains 1 mg of tesamorelin (3). Another vial contains the reconstitution diluent, Sterile Water for Injection. (3)

CONTRAINDICATIONS

- Disruption of the hypothalamic-pituitary axis due to hypophysectomy, hypopituitarism or pituitary tumor/surgery, head irradiation or head trauma (4.1)
- Active malignancy (4.2)
- Known hypersensitivity to tesamorelin and/or mannitol (4.3)
- Pregnancy (4.4)

WARNINGS AND PRECAUTIONS

- Neoplasms: Preexisting malignancy should be inactive and its treatment complete prior to starting EGRIFTA™ therapy. (5.1)
- Elevated IGF-I: Monitor regularly in all patients. Consider discontinuation in patients with persistent elevations. (5.2)
- Fluid retention: May include edema, arthralgia, and carpal tunnel syndrome. (5.3)
- Glucose intolerance: May develop with EGRIFTA™ use. Evaluate glucose status prior to and during therapy with EGRIFTA™. (5.4)
- Hypersensitivity reactions (e.g., rash, urticaria): Advise patients to seek immediate medical attention if suspected. (5.5)
- Injection site reactions: Advise patients to rotate sites. (5.6)
- Acute critical illness: Consider discontinuation. (5.7)

ADVERSE REACTIONS

Most commonly reported adverse reactions (>5% and more frequent than placebo): Arthralgia, injection site erythema, injection site pruritis, pain in extremity, peripheral edema, and myalgia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact EMD Serono at 1-800-283-8088 ext. 5563 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

DRUG INTERACTIONS

- Cytochrome P450-metabolized drugs: Monitor carefully if used with EGRIFTA™. (7.1)

USE IN SPECIFIC POPULATIONS

- Nursing mothers: HIV-1 infected mothers should not human milk-feed to avoid potential postnatal transmission of HIV-1. (8.3)
- Pediatric use: Safety and efficacy not established. (8.4)

See Section 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 11/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

1 INDICATIONS AND USAGE

EGRIFTA™ (tesamorelin for injection) is indicated for the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy *(see Clinical Studies (14))*.

Limitations of Use:

- Since the long-term cardiovascular safety and potential long-term cardiovascular benefit of EGRIFTA™ treatment have not been studied and are not known, careful consideration should be given whether to continue EGRIFTA™ treatment in patients who do not show a clear efficacy response as judged by the degree of reduction in visceral adipose tissue measured by waist circumference or CT scan.
- EGRIFTA™ is not indicated for weight loss management (weight neutral effect).
- There are no data to support improved compliance with anti-retroviral therapies in HIV-positive patients taking EGRIFTA™.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of EGRIFTA™ is 2 mg injected subcutaneously once a day.

The recommended injection site is the abdomen. Injection sites should be rotated to different areas of the abdomen. Do not inject into scar tissue, bruises or the navel.

2.2 Reconstitution Instructions

Instructions for reconstituting EGRIFTA™ are provided in the INSTRUCTIONS FOR USE leaflet enclosed in the EGRIFTA™ medication box and in the injection kit box.

If not used immediately, the reconstituted EGRIFTA™ solution should be discarded. Do not freeze or refrigerate the reconstituted EGRIFTA™ solution.

Reconstituted EGRIFTA™ solution should always be inspected visually for particulate matter and discoloration prior to administration. EGRIFTA™ must be injected only if the solution is clear, colorless and without particulate matter.

3 DOSAGE FORMS AND STRENGTHS

EGRIFTA™ (tesamorelin for injection) is supplied in a vial containing 1 mg of tesamorelin as a lyophilized powder. The diluent (Sterile Water for Injection, 10 mL) is provided in a separate vial.

4 CONTRAINDICATIONS

4.1 Disruption of the Hypothalamic-pituitary Axis

EGRIFTA™ is contraindicated in patients with disruption of the hypothalamic-pituitary axis due to hypophysectomy, hypopituitarism, pituitary tumor/surgery, head irradiation or head trauma.

4.2 Active Malignancy

EGRIFTA™ is contraindicated in patients with active malignancy (either newly diagnosed or recurrent). Any preexisting malignancy should be inactive and its treatment complete prior to instituting therapy with EGRIFTA™.

4.3 Hypersensitivity

EGRIFTA™ is contraindicated in patients with known hypersensitivity to tesamorelin and/or mannitol (an excipient) *[see Warnings and Precautions (5.5)]*.

4.4 Pregnancy

EGRIFTA™ is contraindicated in pregnant women. During pregnancy, visceral adipose tissue increases due to normal metabolic and hormonal changes. Modifying this physiologic change of pregnancy with EGRIFTA™ offers no known benefit and could result in fetal harm. Tesamorelin acetate administration to rats during organogenesis and lactation resulted in hydrocephalus in offspring at a dose approximately two and four times the clinical dose, respectively, based on measured drug exposure (AUC). If pregnancy occurs, discontinue EGRIFTA™ therapy. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus [see Use in Specific Populations (8.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Neoplasms

EGRIFTA™ induces the release of endogenous growth hormone (GH), a known growth factor. Thus, patients with active malignancy should not be treated with EGRIFTA™ *(see Contraindications (4.2)*.

For patients with a history of non-malignant neoplasms, EGRIFTA™ therapy should be initiated after careful evaluation of the potential benefit of treatment. For patients with a history of treated and stable malignancies, EGRIFTA™ therapy should be initiated only after careful evaluation of the potential benefit of treatment relative to the risk of re-activation of the underlying malignancy.

In addition, the decision to start treatment with EGRIFTA™ should be considered carefully based on the increased background risk of malignancies in HIV-positive patients.

5.2 Elevated IGF-I

EGRIFTA™ stimulates GH production and increases serum IGF-I. Given that IGF-I is a growth factor and the effect of prolonged elevations in IGF-I levels on the development or progression of malignancies is unknown, IGF-I levels should be monitored closely during EGRIFTA™ therapy. Careful consideration should be given to discontinuing EGRIFTA™ in patients with persistent elevations of IGF-I levels (e.g., >3 SDS), particularly if the efficacy response is not robust (e.g., based on visceral adipose tissue changes measured by waist circumference or CT scan).

During the clinical trials, patients were monitored every three months. Among patients who received EGRIFTA™ for 26 weeks, 47.4% had IGF-I levels greater than 2 standard deviation scores (SDS), and 35.6% had SDS >3, with this effect seen as early as 13 weeks of treatment. Among those patients who remained on EGRIFTA™ for a total of 52 weeks, at the end of treatment 33.7% had IGF-I SDS >2 and 22.6% had IGF-I SDS >3.

5.3 Fluid Retention

Fluid retention may occur during EGRIFTA™ therapy and is thought to be related to the induction of GH secretion. It manifests as increased tissue turgor and musculoskeletal discomfort resulting in a variety of adverse reactions (e.g. edema, arthralgia, carpal tunnel syndrome) which are either transient or resolve with discontinuation of treatment.

5.4 Glucose Intolerance

EGRIFTA™ treatment may result in glucose intolerance. During the Phase 3 clinical trials, the percentages of patients with elevated HbA_{1c} ($\geq$ 6.5%) from baseline to Week 26 were 4.5% and 1.3% in the EGRIFTA™ and placebo groups, respectively. An increased risk of developing diabetes with EGRIFTA™ (HbA_{1c} level $\geq$ 6.5%) relative to placebo was observed [intent-to-treat hazard odds ratio of 3.3 (CI 1.4, 9.6)]. Therefore, glucose status should be carefully evaluated prior to initiating EGRIFTA™ treatment. In addition, all patients treated with EGRIFTA™ should be monitored periodically for changes in glucose metabolism to diagnose those who develop impaired glucose tolerance or diabetes. Diabetes is a known cardiovascular risk factor and patients who develop glucose intolerance have an elevated risk for developing diabetes. Caution should be exercised in treating HIV-positive patients with lipodystrophy with EGRIFTA™ if they develop glucose intolerance or diabetes, and careful consideration should be given to discontinuing EGRIFTA™ treatment in patients who do not show a clear efficacy response as judged by the degree of reduction in visceral adipose tissue by waist circumference or CT scan measurements.

Since EGRIFTA™ increases IGF-I, patients with diabetes who are receiving ongoing treatment with EGRIFTA™ should be monitored at regular intervals for potential development or worsening of retinopathy.

5.5 Hypersensitivity Reactions

Hypersensitivity reactions may occur in patients treated with EGRIFTA™. Hypersensitivity reactions occurred in 3.6% of patients with HIV-associated lipodystrophy treated with EGRIFTA™ in the Phase 3 clinical trials. These reactions included pruritus, erythema, flushing, urticaria, and other rash. In cases of suspected hypersensitivity reactions, patients should be advised to seek prompt medical attention and treatment with EGRIFTA™ should be discontinued immediately.

5.6 Injection Site Reactions

EGRIFTA™ treatment may cause injection site reactions, including injection site erythema, pruritus, pain, irritation, and bruising. The incidence of injection site reactions was 24.5% in EGRIFTA™-treated patients and 14.4% in placebo-treated patients during the first 26 weeks of treatment in the Phase 3 clinical trials. For patients who continued EGRIFTA™ for an additional 26 weeks, the incidence of injection site reactions was 6.1%. In order to reduce the incidence of injection site reactions, it is recommended to rotate the site of injection to different areas of the abdomen.

5.7 Acute Critical Illness

Increased mortality in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure has been reported after treatment with pharmacologic amounts of growth hormone. EGRIFTA™ has not been studied in patients with acute critical illness. Since EGRIFTA™ stimulates growth hormone production, careful consideration should be given to discontinuing EGRIFTA™ in critically ill patients.

6 ADVERSE REACTIONS

The most commonly reported adverse reactions are hypersensitivity (e.g., rash, urticaria) reactions due to the effect of GH (e.g., arthralgia, extremity pain, peripheral edema, hyperglycemia, carpal tunnel syndrome), injection site reactions (injection site erythema, pruritis, pain, urticaria, irritation, swelling, hemorrhage).

During the first 26 weeks of treatment (main phase), discontinuations as a result of adverse reactions occurred in 9.6% of patients receiving EGRIFTA™ and 6.8% of patients receiving placebo. Apart from patients with hypersensitivity reactions identified during the studies and who were discontinued per protocol (2.2%), the most common reasons for discontinuation of EGRIFTA™ treatment were adverse reactions due to the effect of GH (4.2%) and local injection site reactions (4.6%).

During the following 26 weeks of treatment (extension phase), discontinuations as a result of adverse events occurred in 2.4% of patients in the T-T group (patients treated with tesamorelin for Week 0-26

and with tesamorelin for Week 26-52) and 5.2% of patients in the T-P group (patients treated with tesamorelin for Week 0-26 and with placebo for Week 26-52).

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Seven hundred and forty HIV-infected patients with lipodystrophy and excess abdominal fat were exposed to EGRIFTA™ in the Phase 3 clinical trials; of these 543 received EGRIFTA™ during the initial 26-week placebo-controlled phase *[see Clinical Studies (14)]*.

Adverse reactions that occurred more frequently with EGRIFTA™ relative to placebo and had an incidence ≥1% during the first 26 weeks across all studies are presented in Table 1.

Table 1. Adverse Reactions Reported in ≥ 1% and More Frequent in EGRIFTA™ –treated than Placebo Patients during the 26-Week Main Phase (Combined Studies)

	Incidence of patients (%) with adverse drug reactions	
System Organ Class Preferred Term	EGRIFTA™ (N=543)	Placebo (N=263)
Musculoskeletal and connective tissue disorders		
Arthralgia	13.3	11.0
Pain in extremity	6.1	4.6
Myalgia	5.5	1.9
Musculoskeletal Pain	1.8	0.8
Musculoskeletal stiffness	1.7	0.4
Joint stiffness	1.5	0.8
Muscle spasms	1.1	0.8
Joint swelling	1.1	0.0
General disorders and administration site conditions		
Injection site erythema	8.5	2.7
Injection site pruritus	7.6	0.8
Edema peripheral	6.1	2.3
Injection site pain	4.1	3.0
Injection site irritation	2.9	1.1
Pain	1.7	1.1
Injection site hemorrhage	1.7	0.4
Injection site urticaria	1.7	0.4
Injection site swelling	1.5	0.4
Injection site reaction	1.3	0.8
Chest pain	1.1	0.8
Injection site rash	1.1	0.0
Nervous system disorders		
Paresthesia	4.8	2.3

	Incidence of patients (%) with adverse drug reactions	
System Organ Class Preferred Term	EGRIFTA™ (N=543)	Placebo (N=263)
Hypoesthesia	4.2	1.5
Carpal tunnel syndrome	1.5	0.0
Gastrointestinal disorders		
Nausea	4.4	3.8
Vomiting	2.6	0.0
Dyspepsia	1.7	0.8
Abdominal pain upper	1.1	0.8
Cardiac disorders		
Palpitations	1.1	0.4
Psychiatric disorders		
Depression	2.0	1.5
Skin and subcutaneous tissue disorders		
Rash	3.7	1.5
Pruritus	2.4	1.1
Night sweats	1.1	0.4
Vascular disorders		
Hypertension	1.3	0.8
Injury, poisoning and procedural complications		
Muscle strain	1.1	0.0
Investigations		
Blood creatine phosphokinase increased	1.5	0.4

Mean levels of fasting blood glucose and fasting insulin were not significantly different between EGRIFTA™-treated and placebo-treated patients after 26 weeks of treatment.

In the EGRIFTA™ Phase 3 clinical trials, mean baseline (Week 0) HbA_{1c} was 5.26% among patients in the EGRIFTA™ group and 5.28% among those in the placebo group. At Week 26, mean HbA_{1c} was higher among patients treated with EGRIFTA™ compared with placebo (5.39% vs. 5.28% for the EGRIFTA™ and placebo groups, respectively, mean treatment difference of 0.12%, p=0.0004). Patients receiving EGRIFTA™ had an increased risk of developing diabetes (HbA_{1c} level $\geq$ 6.5%) compared with placebo (4.5% vs. 1.3%), with a hazard ratio of 3.3 (CI 1.4, 9.6).

Adverse reactions observed during Week 26 to 52 of the Phase 3 clinical trials which had an incidence of $\geq$1% and were seen more frequently with EGRIFTA™ relative to placebo are presented in Table 2:

Table 2. Adverse Reactions Reported in ≥ 1% and More Frequent in EGRIFTA™–treated than Placebo Patients during the 26-Week Extension Phase of the Combined Studies (Week 26 to Week 52 of the studies)

	Incidence of patients (%) with adverse drug reactions	
System Organ Class Preferred Term	T-T[1] (Week 26-52) (N=246)	T-P[2](Week 26-52) (N=135)
Musculoskeletal and connective tissue disorders		
Pain in extremity	3.3	0.7
Myalgia	1.2	0.0
General disorders and administration site conditions		
Injection site pruritus	2.0	0.0
Edema peripheral	2.0	0.0
Injection site erythema	1.2	0.0
Nervous system disorders		
Paresthesia	1.6	1.5
Hypoesthesia	1.6	0.7
Neuropathy peripheral	1.6	1.5
Gastrointestinal disorders		
Vomiting	2.0	0.7
Psychiatric disorders		
Depression	1.6	0.7
Insomnia	1.2	0.0
Skin and subcutaneous tissue disorders		
Pruritus	1.2	0.7
Urticaria	1.2	0.0
Night sweats	1.2	0.0
Vascular disorders		
Hypertension	1.6	1.5
Hot flush	1.2	0.7

[1]T-T = tesamorelin for Week-0-26 and tesamorelin for Week 26-52

[2]T-P = tesamorelin for Week-0-26 and placebo for Week 26-52

For patients who continued from Week 26-52, mean levels of fasting blood glucose, fasting insulin, and HbA_{1c} were not different between the T-T and T-P groups.

6.2 Immunogenicity

As with all therapeutic proteins and peptides, there is a potential for in vivo development of anti-EGRIFTA™ antibodies. In the combined Phase 3 clinical trials anti-tesamorelin IgG antibodies were detected in 49.5% of patients treated with EGRIFTA™ for 26 weeks and 47.4% of patients who received EGRIFTA™ for 52 weeks. In the subset of patients with hypersensitivity reactions, anti-tesamorelin IgG antibodies were detected in 85.2%. Cross-reactivity to endogenous growth hormone-releasing hormone

(GHRH) was observed in approximately 60% of patients who developed anti-tesamorelin antibodies. Patients with and without anti-tesamorelin IgG antibodies had similar mean reductions in visceral adipose tissue (VAT) and IGF-I response suggesting that the presence of antibodies did not alter the efficacy of EGRIFTA™. In a group of patients who had antibodies to tesamorelin after 26 weeks of treatment (56%) and were re-assessed 6 months later, after stopping EGRIFTA™ treatment, 18% were still antibody positive.

Neutralizing antibodies to tesamorelin and hGHRH were detected in vitro at Week 52 in 10% and 5% of EGRIFTA™-treated patients, respectively. They did not appear to have an impact on efficacy, as evidenced by comparable changes in VAT and IGF-I level in patients with or without in vitro neutralizing antibodies.

The observed incidence of antibody positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, methodology, sample handling, timing of sample collection, concomitant medication and underlying disease. For these reasons, comparison of the incidence of antibodies to EGRIFTA™ with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

7.1 Cytochrome P450-Metabolized Drugs

Co-administration of EGRIFTA™ with simvastatin, a sensitive CYP3A substrate, showed that EGRIFTA™ had no significant impact on the pharmacokinetics profiles of simvastatin in healthy subjects. This result suggests that EGRIFTA™ may not significantly affect CYP3A activity. Other isoezymes of CYP450 have not been evaluated with EGRIFTA™. Published data, however, indicate that GH may modulate cytochrome P450 (CYP450) mediated antipyrine clearance in man. These data suggest that GH may alter the clearance of compounds known to be metabolized by CYP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporine). Because tesamorelin stimulates GH production, careful monitoring is advisable when EGRIFTA™ is administered in combination with other drugs known to be metabolized by CYP450 liver enzymes [*see Clinical Pharmacology (12.3)*].

7.2 11β-Hydroxysteroid Dehydrogenase Type 1 (11βHSD-1)

GH is known to inhibit 11β-hydroxysteroid dehydrogenase type 1 (11βHSD-1), a microsomal enzyme required for conversion of cortisone to its active metabolite, cortisol, in hepatic and adipose tissue. Because tesamorelin stimulates GH production, patients receiving glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in maintenance or stress doses following initiation of EGRIFTA™, particularly in patients treated with cortisone acetate and prednisone because conversion of these drugs to their biologically active metabolites is dependent on the activity of 11βHSD-1.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [see Contraindications (4.4)].
EGRIFTA™ is contraindicated in pregnant women. During pregnancy, visceral adipose tissue increases due to normal metabolic and hormonal changes. Modifying this physiologic change of pregnancy with EGRIFTA™ offers no known benefit and could result in fetal harm. Tesamorelin acetate administration to rats during organogenesis and lactation resulted in hydrocephaly in offspring at a dose of approximately two and four times the clinical dose, respectively, based on measured drug exposure (AUC). If pregnancy occurs, discontinue EGRIFTA™ therapy. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Tesamorelin acetate administration to rats during organogenesis and lactation produced hydrocephaly in offspring at a dose of approximately two and four times the clinical dose, respectively, based on measured drug exposure (AUC). Actual animal dose was 1.2 mg/kg. During organogenesis, lower doses approximately 0.1 to 1 times the clinical dose caused delayed skull ossification in rats. Actual animal doses were 0.1 to 0.6 mg/kg. No adverse developmental effects occurred in rabbits using doses up to approximately 500 times the clinical dose.

8.2 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers in the United States not human milk-feed their infants to avoid risking postnatal transmission of HIV-1 infection. Because of both the potential for HIV-1 infection transmission and serious adverse reactions in nursing infants, mothers receiving EGRIFTA™ should be instructed not to human milk-feed.

It is not known whether EGRIFTA™ is excreted in human milk. Tesamorelin acetate administration to rats during organogenesis and lactation resulted in hydrocephaly in offspring at a dose of approximately two and four times the clinical dose, respectively, based on measured drug exposure (AUC). Actual animal dose was 1.2 mg/kg.

8.3 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. EGRIFTA™ should not be used in children with open epiphyses, among whom excess GH and IGF-I may result in linear growth acceleration and excessive growth.

8.4 Geriatric Use

There is no information on the use of EGRIFTA™ in patients greater than 65 years of age with HIV and lipodystrophy.

8.5 Renal and Hepatic Impairment

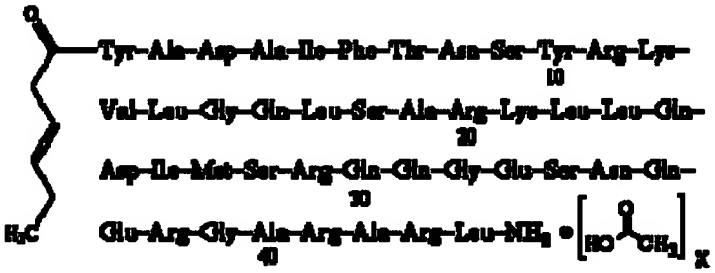
Safety, efficacy, and pharmacokinetics of EGRIFTA™ in patients with renal or hepatic impairment have not been established.

10 OVERDOSAGE

No data are available on overdosage.

11 DESCRIPTION

EGRIFTA™ contains tesamorelin (as the acetate salt), an analog of human growth hormone-releasing factor (GRF). The peptide precursor of tesamorelin acetate is produced synthetically and is comprised of the 44 amino acid sequence of human GRF. Tesamorelin acetate is made by attaching a hexenoyl moiety, a C6 chain with a double bond at position 3, to the tyrosine residue at the N-terminal part of the molecule. The molecular formula of tesamorelin acetate is $C_{221}H_{366}N_{72}O_{67}S \cdot x\ C_2H_4O_2$ ($x \approx 7$) and its molecular weight (free base) is 5135.9 Daltons. The structural formula of tesamorelin acetate is:



EGRIFTA™ is a sterile, white to off-white, preservative-free lyophilized powder for subcutaneous injection. After reconstitution with the supplied diluent (Sterile Water for Injection, USP), a solution of EGRIFTA™ is clear and colorless. Each single-use vial of EGRIFTA™ contains 1 mg of tesamorelin as the free base (1.1 mg tesamorelin acetate, anhydrous) and the following inactive ingredient: 50 mg mannitol, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of action

In vitro, tesamorelin binds and stimulates human GRF receptors with similar potency as the endogenous GRF. *[See Clinical Pharmacology (12.2)].*

Growth Hormone-Releasing Factor (GRF), also known as growth hormone-releasing hormone (GHRH), is a hypothalamic peptide that acts on the pituitary somatotroph cells to stimulate the synthesis and pulsatile release of endogenous growth hormone (GH), which is both anabolic and lipolytic. GH exerts its effects by interacting with specific receptors on a variety of target cells, including chondrocytes, osteoblasts, myocytes, hepatocytes, and adipocytes, resulting in a host of pharmacodynamic effects. Some, but not all these effects, are primarily mediated by IGF-I produced in the liver and in peripheral tissues.

12.2 Pharmacodynamics

Effects on IGF-I and IGFBP-3 levels

Tesamorelin stimulates growth hormone secretion, and subsequently increases IGF-I and IGFBP-3 levels. *[See Clinical Studies (14)].*

Other Pituitary Hormones

No clinically significant changes in the levels of other pituitary hormones, including thyroid-stimulating hormone (TSH), luteinizing hormone (LH), adrenocorticotropic hormone (ACTH) and prolactin, were observed in subjects receiving EGRIFTA™ in Phase 3 clinical trials.

12.3 Pharmacokinetics

Absorption

The absolute bioavailability of EGRIFTA™ after subcutaneous administration of a 2 mg dose was determined to be less than 4% in healthy adult subjects. Single and multiple dose pharmacokinetics of EGRIFTA™ have been characterized in healthy subjects and HIV-infected patients without lipodystrophy following 2 mg subcutaneous administration.

The mean values [coefficient of variation (CV)] of the extent of absorption (AUC) for tesamorelin were 634.6 (72.4) and 852.8 (91.9) pg.h/mL in healthy subjects and HIV-infected patients, respectively, after a single subcutaneous administration of a 2 mg EGRIFTA™ dose. The mean (CV) peak tesamorelin concentration (C_{max}) values were 2874.6 (43.9) pg/mL in healthy subjects and 2822.3 (48.9) pg/mL in HIV-infected patients. The median peak plasma tesamorelin concentration (T_{max}) was 0.15 h in both populations.

Distribution

The mean volume of distribution (±SD) of tesamorelin following a single subcutaneous administration was 9.4±3.1 L/kg in healthy subjects and 10.5±6.1 L/kg in HIV-infected patients.

Metabolism

No formal metabolism studies have been performed in humans.

Elimination

Mean elimination half-life ($T_{1/2}$) of tesamorelin was 26 and 38 minutes in healthy subjects and HIV-infected patients, respectively, after subcutaneous administration for 14 consecutive days.

Drug Interactions

Simvastatin

The effect of multiple dose administration of EGRIFTA™ (2 mg) on the pharmacokinetics of simvastatin and simvastatin acid was evaluated in healthy subjects. Co-administration of EGRIFTA™ and simvastatin (a sensitive CYP3A substrate) resulted in 8% decrease in extent of absorption (AUC_{inf}) and 5% increase in rate of absorption (C_{max}) of simvastatin. For simvastatin acid there was a 15% decrease in AUC_{inf} and 1% decrease in C_{max} [*see Drug Interactions (7.1)*].

Ritonavir

The effect of multiple dose administration of EGRIFTA™ (2 mg) on the pharmacokinetics of ritonavir was evaluated in healthy subjects. Co-administration of EGRIFTA™ with ritonavir resulted in 9% decrease in AUC_{inf} and 11% decrease in C_{max} of ritonavir [*see Drug Interactions*].

Specific Populations

Pharmacokinetics of tesamorelin in patients with renal or, hepatic impairment, in pediatric patients, or in elderly patients has not been established.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Life-time carcinogenicity studies in rodents have not been conducted with tesamorelin acetate. No potential mutagenicity of tesamorelin acetate was revealed in a battery of tests including induction of gene mutations in bacteria (the Ames test), gene mutations in mammalian cells grown in vitro (hamster CHOK1 cells), and chromosomal damage in intact animals (bone marrow cells in mice). There was no effect on fertility in male or female rats following administration of tesamorelin acetate at doses up to 0.6 mg/kg (approximately equal to clinical exposure) for 28 days in males or 14 days in females. In the 26-week toxicity study in rats, females given approximately 16 and 25 times the clinical dose were more likely to be in diestrus.

14 CLINICAL STUDIES

Two multicenter, randomized, double-blind, placebo-controlled studies were conducted in HIV-infected patients with lipodystrophy and excess abdominal fat (abdominal lipohypertrophy). Both studies (Study 1 and 2) consisted of a 26-week Main Phase and a 26-week Extension Phase. Main inclusion criteria were age 18-65 years, a waist circumference ≥95 cm (37.4 inches) and a waist-to-hip ratio ≥0.94 for men and ≥94 cm (37.0 inches) and ≥0.88 for women, respectively, and fasting blood glucose (FBG) <150 mg/dL (8.33 mmol/L). Main exclusion criteria included BMI ≤ 20 kg/m^2, type 1 diabetes, type 2 diabetes, if previously treated with insulin or with oral hypoglycemic or insulin-sensitizing agents, history of malignancy, and hypopituitarism. Patients were on a stable anti-retroviral regimen for at least 8 weeks prior to randomization. Patients meeting the inclusion/exclusion criteria were randomized in a 2:1 ratio to

receive 2 mg EGRIFTA™ or placebo subcutaneously daily for 26 weeks. The primary efficacy assessment for each of these studies was the percent change from baseline to Week 26 (Main Phase) in visceral adipose tissue (VAT), as assessed by computed tomography (CT) scan at L4-L5 vertebral level. Secondary endpoints included changes from baseline in patient-reported outcomes related to body image, triglycerides, ratio of total cholesterol to HDL cholesterol, IGF-I levels, and safety parameters. Other endpoints included changes from baseline in waist circumference, abdominal subcutaneous tissue (SAT), trunk fat, and lean body mass. In both studies, EGRIFTA™-treated patients completing the 26-week treatment period were re-randomized to blinded therapy with either daily placebo or 2 mg EGRIFTA™ for an additional 26-week treatment period (Extension Phase) in order to assess maintenance of VAT reduction and to gather long-term safety data. For inclusion in the Extension Phase studies, subjects must have completed the Main Phase with FBG $\leq$ 150 mg/dL.

Main Phase (Baseline to Week 26):

Study 1

This study randomized 412 HIV-infected patients with lipodystrophy and excess abdominal fat to receive either EGRIFTA™ (N=273) or placebo (N=137). At baseline for the two groups combined, mean age was 48 years; 86% were male; 75% were white, 14% were Black/African American, and 8% were Hispanic; mean weight was 90 kg; mean BMI was 29 kg/m^2; mean waist circumference was 104 cm; mean hip circumference was 100 cm; mean VAT was 176 cm^2; mean CD4 cell count was 606 $cells/mm^3$; 69% had undetectable viral load (<50 copies/mL); and 33.7% randomized to EGRIFTA™ and 36.6% randomized to placebo had impaired glucose tolerance, while 5.6% randomized to EGRIFTA™ and 6.7 % randomized to placebo had diet-controlled diabetes mellitus. The twenty-six week completion rate in Study 1 was 80%.

Study 2

This study randomized 404 HIV-infected patients with lipodystrophy and excess abdominal fat to receive either EGRIFTA™ (N=270) or placebo (N=126). At baseline for the two groups combined, mean age was 48 years; 84% were male; 77% were white, 12% were Black/African American, and 9% were Hispanic; mean weight was 88 kg; mean BMI was 29 kg/m^2; mean waist circumference was 105 cm; mean hip circumference was 100 cm; mean VAT was 189 cm^2; mean CD4 cell count was 592 $cells/mm^3$; 83% had undetectable viral load (<50 copies/mL); and 44.1 % randomized to EGRIFTA™ and 39.7% randomized to placebo had impaired glucose tolerance, while 9.3% randomized to EGRIFTA™ and 9.5 % randomized to placebo had diet-controlled diabetes mellitus. The twenty-six week completion rate in Study 2 was 74%.

Results for the Main Phases of Studies 1 and 2 are presented in Tables 3 and 4.

Table 3: Changes from Baseline to Week 26 in Visceral Adipose Tissue (cm^2) by Treatment Group (Intent-To-Treat Population with Last Observation Carried Forward)

MAIN PHASE (Baseline-Week 26)				
	Study 1		Study 2	
	EGRIFTA™ (N=273)	Placebo (N=137)	EGRIFTA™ (N=270)	Placebo (N=126)
Baseline (cm^2)	178 (77)	171 (77)	186 (87)	195 (95)
Change (cm^2)	-27	4	-21	-0
Mean treatment difference (95% CI)	-31 (-39,-24)		-21 (-29,-12)	
Mean Change (%)[1]	-18	2	-14	-2
Mean Treatment difference (95% CI)[1]	-20 (-24, -15)		-12 (-16, -7)	

Baseline data are expressed as mean (SD); Change refers to least-squares means (LSM); CI: confidence interval.

[1] Results derived from the statistical model: Ln(VAT Week 26/VAT Baseline) = Ln(VAT Baseline) + treatment group

Table 4: Changes from Baseline to Week 26 in IGF-I, IGFBP-3, Weight, and Waist Circumference by Treatment Group (Intent-To-Treat Population with Last Observation Carried Forward)

MAIN PHASE (Baseline-Week 26)					
		Study 1		Study 2	
		EGRIFTA™ (N=273)	Placebo (N=137)	EGRIFTA™ (N=270)	Placebo (N=126)
IGF-I (ng/mL)	Baseline	161 (59)	168 (75)	146 (66)	149 (59)
	Change	107	-15	108	3
	Mean treatment difference (95% CI)	122 (101, 141)		105 (85, 126)	
IGFBP-3 (mg/L)	Baseline	3 (1)	3 (1)	3 (1)	3 (1)
	Change	0.4	-0.2	0.8	-0.0
	Mean treatment difference (95% CI)	0.6 (0.5, 0.8)		0.8 (0.5, 1.0)	
Weight (kg)	Baseline	90 (14)	90 (14)	89 (14)	87 (16)
	Change	-0.4	0.0	0.5	0.3
	Mean treatment difference (95% CI)	-0.4 (-1.3, 0.5)		0.2 (-0.7, 1.3)	
Waist Circumference (cm)	Baseline	104 (10)	105 (9)	105 (9)	105 (9)
	Change	-3 (5)	-1 (4)	-2 (5)	-1 (5)
	Mean treatment difference (95% CI)	-2 (-2.8, -0.9)		-1 (-2.5, -0.3)	

Baseline data are expressed as mean (SD); Change refers to least-squares means (LSM); CI: confidence interval.

A subgroup analysis by gender showed that there were no statistical differences in the percent change from baseline in visceral adipose tissue (VAT) and IGF-I responses, respectively, between males and females.

At Week 26, treatment with EGRIFTA™ resulted in a reduction from baseline in mean trunk fat of 1.0 kg in Study 1 and 0.8 kg in Study 2, respectively (compared with an increase of 0.4 kg in Study 1 and of 0.2 kg in Study 2, respectively, in patients receiving placebo). Treatment with EGRIFTA™ resulted in an increase from baseline in mean lean body mass of 1.3 kg in Study 1 and of 1.2 kg in Study 2, respectively (compared with a decrease of 0.2 kg in Study 1 and of 0.03 kg in Study 2, respectively, in patients receiving placebo).

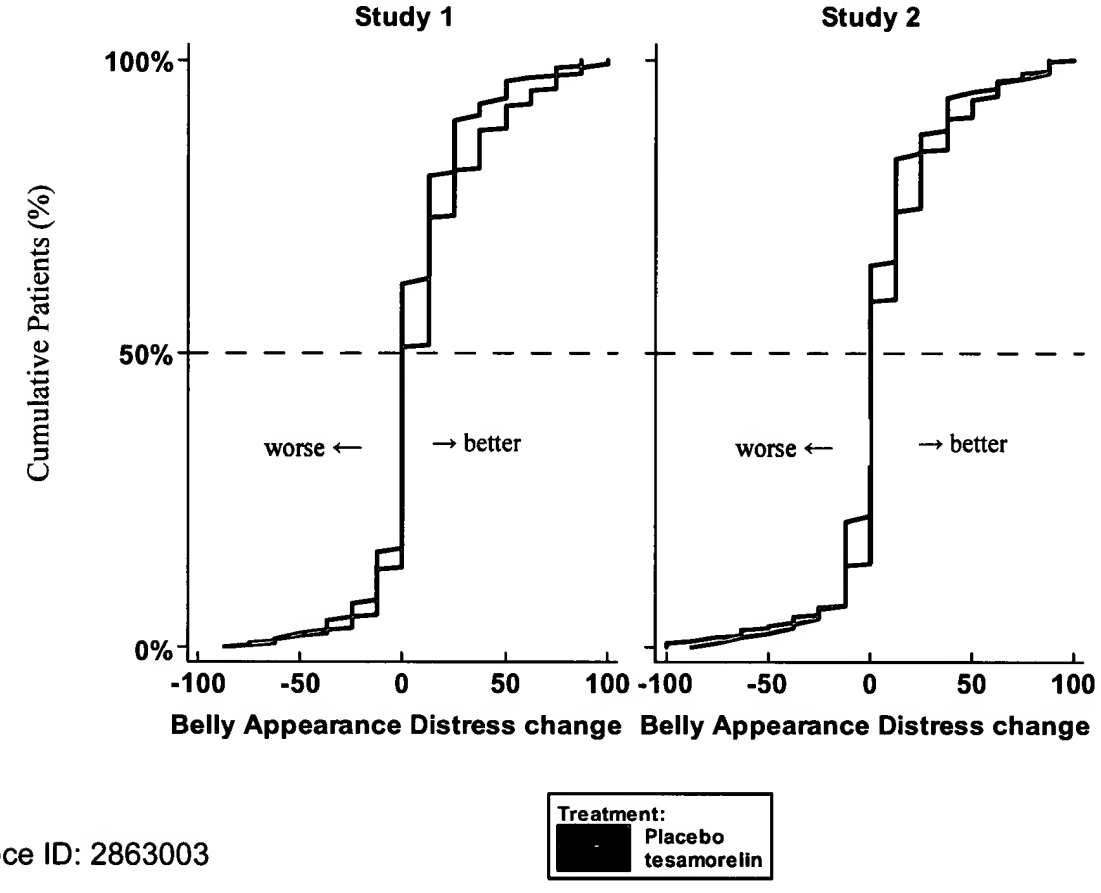
On average, there were no adverse effects of EGRIFTA™ on lipids or subcutaneous adipose tissue (SAT). EGRIFTA™ did not adversely alter antiretroviral effectiveness, such as mean circulating levels of CD4 counts or HIV-1 RNA (viral load).

Patient Reported Outcomes

Patients rated the degree of distress associated with their belly appearance on a 9-point rating scale that was then transformed to a score from 0 (extremely upsetting and distressing) to 100 (extremely encouraging). A score of 50 indicated neutral (no feeling either way). A positive change from baseline score indicated improvement, i.e., less distress.

The cumulative distribution of response (change from baseline to 26 weeks) is shown in Figure 1 for both treatment groups. A curve shifted to the right on this scale indicates a greater percentage of patients reporting improvement.

Figure 1. Cumulative Distribution of Response for Belly Appearance Distress



Extension Phase (Weeks 26-52):

In the double-blind Extension Phase, patients on EGRIFTA™ completing the 26-week Main Phase were re-randomized to receive 2 mg EGRIFTA™ or placebo.

Study 1

This study re-randomized 207 HIV-infected patients with lipodystrophy who completed EGRIFTA™ treatment in the Main Phase to receive either EGRIFTA™ (N=154) or placebo (N=50) for an additional 26-week duration (3:1 randomization ratio). At baseline (Week 26) for the two groups combined, mean age was 48 years; 88% were male; 78% were white, 12% were Black/African American, and 8% were Hispanic; mean weight was 90 kg; mean BMI was 29 kg/m^2; mean waist circumference was 102 cm; mean hip circumference was 100 cm; mean VAT was 145 cm^2; mean CD4 cell count was 639 $cells/mm^3$; 68% had undetectable viral load (<50 copies/mL); and and for those EGRIFTA™-treated patients completing the 26-week treatment period that were re-randomized to EGRIFTA™ (T-T group) or re-randomized to placebo, 36.6 % and 32.0 %, respectively, had impaired glucose tolerance , while 2.0 % re-randomized to EGRIFTA™ and 6.0 % re-randomized to placebo had diet-controlled diabetes mellitus. The completion rate for patients randomized into the extension phase of Study 1 was 83%.

Study 2

This study re-randomized 177 HIV-infected patients with lipodystrophy who completed EGRIFTA™ treatment in the Main Phase to receive either EGRIFTA™ (N=92) or placebo (N=85) for an additional 26-week duration (1:1 randomization ratio). At baseline (Week 26) for the two groups combined, mean age was 48 years; 90% were male; 84% were white, 9% were Black/African American, and 7% were Hispanic; mean weight was 89 kg; mean BMI was 28 kg/m^2; mean waist circumference was 105 cm; mean hip circumference was 100 cm;; mean VAT was 172 cm^2; mean CD4 cell count was 579 $cells/mm^3$; 82% had undetectable viral load (<50 copies/mL); and for those EGRIFTA™-treated patients completing the 26-week treatment period that were re-randomized to EGRIFTA™ (T-T group) or re-randomized to placebo, 48.9 % and 50.6 %, respectively, had impaired glucose tolerance, while 4.3 % re-randomized to EGRIFTA™ and 12.9 % re-randomized to placebo had diet-controlled diabetes mellitus. The completion rate for patients randomized into the extension phase of Study 2 was 81%.

Results for the Extension Phases of Studies 1 and 2 are presented in Tables 5 and 6.

Table 5: Changes from Week 26 Baseline to Week 52 in Visceral Adipose Tissue (cm^2) by Treatment Group (Intent-To-Treat Population with Last Observation Carried Forward)

EXTENSION PHASE (Week 26-52)				
	Study 1		Study 2	
	T-T[1] (Week 26-52) (N=154)	T-P[2] (Week 26-52) (N=50)	T-T[1] (Week 26-52) (N=92)	T-P[2] (Week 26-52) (N=85)
Week 26 (cm^2)	145 (72)	144 (72)	166 (89)	177 (88)
Change (cm^2)	3	25	-11	24
Mean treatment difference (95% CI)	-22 (-34, -10)		-35 (-48, -22)	
Mean Change (%)[1]	0	22	-5	16
Mean treatment difference (95% CI)[3]	-17 (-24, -10)		-18 (-24, -11)	

Week 26 baseline data are expressed as mean (SD). Change refers to least-squares means (LSM); CI: confidence interval.

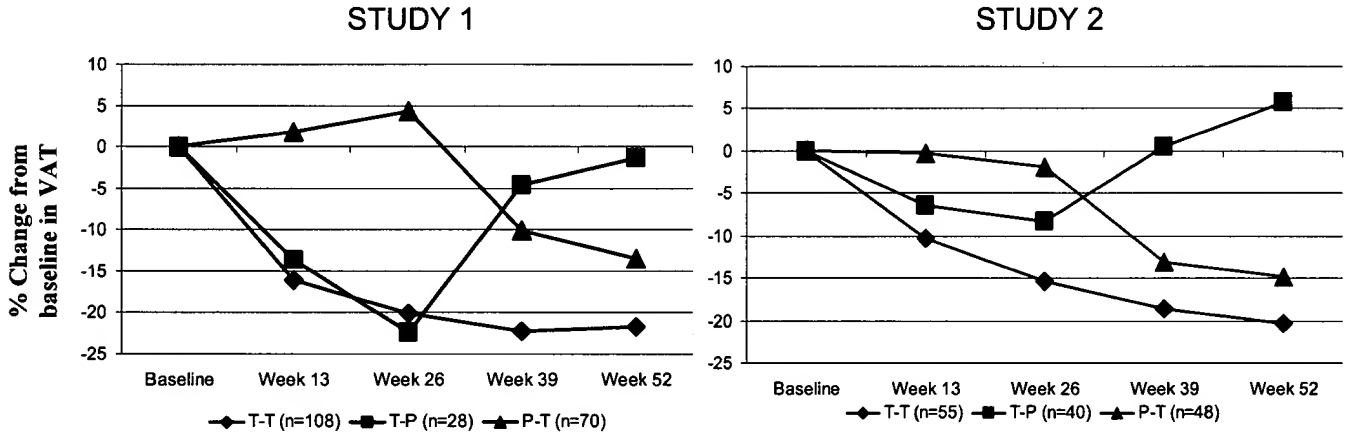
[1]T-T = tesamorelin for Weeks 0-26 and tesamorelin for Weeks 26-52

[2]T-P = tesamorelin for Weeks 0-26 and placebo for Weeks 26-52

[3]Results derived from the statistical model: Ln(VAT Week 52/Week 26) = Ln(Week 26 VAT) + treatment group

Figure 2 shows the percent change in VAT from baseline (Week 0) over time until 52 weeks in completer patients.

Figure 2 Percent Change from Baseline in VAT over Time



Data in Figure 2 are expressed as mean values. T-T (tesamorelin to tesamorelin) refers to the group of patients who received tesamorelin for Weeks 0-26 and were re-randomized to tesamorelin for Weeks 26-52. T-P (tesamorelin to placebo) refers to the group of patients who received tesamorelin for Weeks 0-26 and were re-randomized to placebo for Weeks 26-52. P-T (placebo to tesamorelin) refers to the group of

patients who received placebo for Weeks 0-26 and were switched to tesamorelin (treated open label) for Weeks 26-52.

Table 6: Changes from Week 26 Baseline to Week 52 in IGF-I, IGFBP-3, Weight, and Waist Circumference by Treatment Group (Intent-To-Treat Population with Last Observation Carried Forward)

EXTENSION PHASE (Weeks 26-52)					
		Study 1		Study 2	
		T-T[1] (Week 26-52) (N=154)	T-P[2] (Week 26-52) (N=50)	T-T[1] (Week 26-52) (N=92)	T-P[2] (Week 26-52) (N=85)
IGF-I (ng/mL)	Week 26	291 (124)	281 (105)	280 (134)	269 (110)
	Change	-59	-137	-25	-135
	Mean treatment difference (95% CI)	78 (50, 106)		110 (87, 134)	
IGFBP-3 (mg/L)	Week 26	3 (1)	3 (1)	3 (1)	3 (1)
	Change	-0.2	-0.5	-0.3	-0.9
	Mean treatment difference (95% CI)	0.3 (-0.0, 0.6)		0.6 (0.3, 0.9)	
Weight (kg)	Week 26	89 (14)	92 (17)	89 (13)	90 (14)
	Change	0.2	0.6	-0.5	0.1
	Mean treatment difference (95% CI)	-0.4 (-2, 1)		-0.6 (-2, 1)	
Waist Circumference (cm)	Week 26	101(10)	102 (12)	101 (9)	103 (11)
	Change	-0.2	2.4	-1.1	0.2
	Mean treatment difference (95% CI)	-2.6 (-4, -1)		-1.3 (-2, 0)	

Week 26 baseline data are expressed as mean (SD); Change refers to least-square means (LSM); CI: confidence interval.

[1]T-T = tesamorelin for Week-0-26 and tesamorelin for Week 26-52

[2]T-P = tesamorelin for Week-0-26 and placebo for Week 26-52

Patients treated with EGRIFTA™ for 52 weeks (T-T group) showed no change between Weeks 26 and 52 in mean trunk fat (increase of 0.1 kg in Study 1 and decrease of 0.5 kg in Study 2, respectively, compared with an increase of 1.4 kg in patients in the T-P group in Study 1 and an increase of 1.09 kg in Study 2, respectively) nor was there a change from Week 26 baseline in mean lean body mass (decrease of 0.1 kg in Study 1 and increase of 0.1 kg in Study 2, respectively, compared with a decrease of 1.8 kg in patients in the T-P group in Study 1 and a decrease of 1.7 kg in Study 2, respectively).

There was no adverse effect of EGRIFTA™ on lipids or subcutaneous adipose tissue (SAT). EGRIFTA™ did not adversely alter antiretroviral effectiveness, such as mean circulating levels of CD4 counts or HIV-1 RNA (viral load).

16 HOW SUPPLIED/STORAGE AND HANDLING

EGRIFTA™ (tesamorelin for injection) is supplied as a sterile, white to off-white lyophilized powder. Each single-use vial of EGRIFTA™ contains 1 mg of tesamorelin as the free base (1.1 mg tesamorelin acetate, anhydrous) and the following inactive ingredient: 50 mg mannitol, USP.

EGRIFTA™ is available in a package comprised of two boxes. One box contains 60 vials of EGRIFTA™ and a second box contains 30 single-use 10 mL vials of reconstitution diluent (Sterile Water for Injection, USP), disposable syringes, and needles sufficient for a 30 day supply.

After reconstitution with Sterile Water for Injection, the reconstituted solution concentration is 1 mg/mL and should be injected immediately.

EGRIFTA™ vials should be protected from light and be kept in the original box until time of use. Non-reconstituted EGRIFTA™ must be stored at refrigerated temperature, between 2°C and 8°C (36°F and 46°F). The reconstitution diluent (Sterile Water for Injection, USP), syringes and needles should be stored at controlled room temperature of 20°C to 25°C (68°F to 77°F).

Syringes and needles are for single-use by a single patient and should never be shared between patients.

NDC 44087-2010-3

17 PATIENT COUNSELING INFORMATION

- Fluid retention (5.3) – Advise patients that treatment with EGRIFTA™ may cause symptoms consistent with fluid retention, including edema, arthralgia, and carpal tunnel syndrome. These reactions are either transient or resolve with discontinuation of treatment.
- Hypersensitivity Reactions (5.5) – Advise patients that hypersensitivity reactions (e.g., rash, urticaria) may occur during treatment with EGRIFTA™. Advise patients to seek prompt medical attention and to immediately discontinue treatment with EGRIFTA™.
- Injection Site Reactions (5.6) – Advise patients of possible injection site reactions, including injection site erythema, pruritus, pain, irritation, and bruising. To reduce the incidence of injection site reactions, advise patients to rotate the site of injection.
- Counsel patients that they should never share an EGRIFTA™ syringe with another person, even if the needle is changed. Sharing of syringes or needles between patients may pose a risk of transmission of infection.

Pregnancy

Advise women to discontinue EGRIFTA™ if pregnancy occurs, as the drug offers no known benefit to pregnant women and could result in fetal harm *[see Contraindications (4.4) and Use in Specific Populations (8.1)]*.

Nursing Mothers

Because of both the potential for HIV-1 infection transmission and serious adverse reactions in nursing infants, mothers receiving EGRIFTA™ should be instructed not to human milk-feed *[see Use in Specific Populations (8.2)]*.

Patient Information

EGRIFTA™ (eh-GRIF-tuh)

(tesamorelin for injection) for subcutaneous use

Read the Patient Information that comes with EGRIFTA™ before you start to take it and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What Is EGRIFTA™?

- EGRIFTA™ is an injectable prescription medicine to reduce the excess in abdominal fat in HIV-infected patients with lipodystrophy. EGRIFTA™ contains a growth hormone-releasing factor (GRF).
- the impact and safety of EGRIFTA™ on cardiovascular health has not been studied.
- EGRIFTA™ is not indicated for weight loss management.
- it is not known whether taking EGRIFTA™ helps improve compliance with anti-retroviral medications.
- it is not known if EGRIFTA™ is safe and effective in children. EGRIFTA™ is not recommended to be used in children.

Who should not use EGRIFTA™?

Do not use EGRIFTA™ if you:

- have pituitary gland tumor, pituitary gland surgery or other problems related to your pituitary gland.
- have or had a history of active cancer (either newly diagnosed or recurrent).
- are allergic to tesamorelin or any of the ingredients in EGRIFTA™. See the end of this leaflet for a complete list of ingredients in EGRIFTA™.
- are pregnant or become pregnant. If you become pregnant, stop using EGRIFTA™ and talk with your healthcare provider. See "What should I tell my healthcare provider before using EGRIFTA™?"

What should I tell my healthcare provider before using EGRIFTA™?

Before using EGRIFTA™, tell your healthcare provider if you:

- have or have had cancer
- have diabetes
- are breastfeeding or plan to breastfeed. It is not known if EGRIFTA™ passes into your breast milk. The Centers for Disease Control and Prevention (CDC) recommends that HIV-infected mothers not breastfeed to avoid the risk of passing HIV infection to your baby. Talk with your healthcare provider about the best way to feed your baby if you are taking EGRIFTA™.

- have kidney or liver problems
- have any other medical condition.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. EGRIFTA™ may affect the way other medicines work, and other medicines may affect how EGRIFTA™ works.

Know the medicines you take. Keep a list with you to show your healthcare provider and pharmacist when you get a new medicine.

How should I use EGRIFTA™?

- **Read the detailed "Instructions for Use"** that comes with EGRIFTA™ before you start using EGRIFTA™. Your healthcare provider will show you how to inject EGRIFTA™.
- Use EGRIFTA™ exactly as prescribed by your healthcare provider.
- Inject EGRIFTA™ under the skin (subcutaneously) of your stomach area (abdomen).
- Change (rotate) the injection site on your stomach area (abdomen) with each dose. Do not inject EGRIFTA™ into scar tissue, bruises or your navel.
- **Do not** share needles or syringes with other people. Sharing of needles can result in the transmission of infectious diseases, such as HIV.

What are the possible side effects of EGRIFTA™?

EGRIFTA™ may cause serious side effects including:

- **Serious allergic reaction.** Some people taking EGRIFTA™ may have an allergic reaction.

  Stop using EGRIFTA™ and get emergency help right away if you have any of the following symptoms:

  - a rash over your body
  - hives
  - swelling of your face or throat
  - shortness of breath or trouble breathing
  - fast heartbeat
  - feeling of faintness or fainting

- **Swelling (fluid retention).** EGRIFTA™ can cause swelling in some parts of your body. Call your healthcare provider if you have an increase in joint pain, or pain or numbness in your hands or wrist (carpal tunnel syndrome).
- **Increase in glucose (blood sugar) intolerance and diabetes.** Your healthcare provider will measure your blood sugar periodically.

- **Injection site reactions.** Change (rotate) your injection site to help lower your risk for injection site reactions. Call your healthcare provider for medical advice if you have the following symptoms around the area of the injection site:
  - redness
  - itching
  - pain
  - irritation
  - bleeding
  - rash
  - swelling

The most common side effects of EGRIFTA™ include:

- joint pain
- pain in legs and arms
- swelling in your legs
- muscle soreness
- tingling, numbness and pricking
- nausea
- vomiting
- rash
- itching

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of EGRIFTA™. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. To report side effects, contact EMD Serono toll-free at 1-800-283-8088 ext. 5563. You may report side effects to FDA at 1-800-FDA-1088.

How do I store EGRIFTA™?

- EGRIFTA™ has two boxes
  - Store the Medication Box of EGRIFTA™ vials in the refrigerator between 2°C and 8°C (36°F and 46°F).
  - Store the box of Sterile Water for Injection, syringes and needles at room temperature between 20°C to 25°C (68°F to 77°F).
- Keep EGRIFTA™ vials in Medication Box away from light.
- Do not freeze.
- Do not use EGRIFTA™ after the expiration date printed on the carton and vial labels.
- After mixing, use EGRIFTA™ right away and throw away any unused EGRIFTA™. Do not store mixed EGRIFTA™. Also, throw away the used vial of Sterile Water for Injection.

Keep EGRIFTA™ and all medicines out of the reach of children.

General information about the safe and effective use of EGRIFTA™

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use EGRIFTA™ for a condition for which it was not prescribed. Do not give EGRIFTA™ to other people, even if they have the same symptoms you have. It may harm them.

Do not share your EGRIFTA™ syringe with another person, even if the needle is changed. Do not share your EGRIFTA™ needles with another person.

This Patient Information leaflet summarizes the most important information about EGRIFTA™. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about EGRIFTA™ that is written for healthcare professionals.

For more information about EGRIFTA™, go to www.EGRIFTA.com or contact AXIS Center toll-free at 1-877-714-2947.

What are the ingredients in EGRIFTA™?

Active ingredient: tesamorelin
Inactive ingredients: mannitol and Sterile Water for Injection

EMD Serono EMD

EGRIFTA™ is a trademark of Theratechnologies Inc.

Distributed by: EMD Serono, Inc., Rockland, MA 02370, USA

Date: 2010-09-27

Patient Instructions for Use

EGRIFTA™ (eh-GRIF-tuh)

(tesamorelin for injection)

202320 EN-2562

Be sure that you read, understand, and follow these Patient Instructions for Use before using EGRIFTA™. Your healthcare provider should show you how to mix and inject EGRIFTA™ before you inject it for the first time. Ask your healthcare provider if you have any questions.

Keep this leaflet in case you need to look at it again later.

Important information for use of EGRIFTA™

- After mixing EGRIFTA™ with Sterile Water for Injection, it should look clear and colorless, with no particles in it. Do not use EGRIFTA™ if it looks cloudy, discolored, or if you see particles in it. Talk to your healthcare provider if you have any questions.
- Do not use EGRIFTA™ after the date on the Medication Box and EGRIFTA™ vial.
- Do not use a syringe or needle more than 1 time.
- Do not share your EGRIFTA™ needles with another person. Sharing of needles can result in the transmission of infectious diseases, such as HIV. Do not share your EGRIFTA™ syringe with another person, even if the needle is changed.
- If you are missing any supplies from your Medication Box or Injection Box, or if anything looks damaged call your pharmacist or contact AXIS Center toll-free at 1-877-714-2947 right away.

Preparing for your EGRIFTA™ injection

- Find a well-lit, clean, and flat surface, such as a table.
- Gather your supplies:
  - Medication Box that contains 60 EGRIFTA™ powder vials
  - Injection Box that contains the following:
    a) 30 10-mL bottles of Sterile Water for Injection, used for mixing
    b) 30 sterile 3-mL syringes with sterile needle already attached (BD 3 mL Syringe)
    c) 30 individual 1½" 18-gauge sterile needles, used for mixing (BD Blunt Fill Needle)
    d) 30 individual ½" 27-gauge injection needles (BD Eclipse™ Injection Needle)
  - Alcohol pads
  - Sterile gauze
  - A "sharps container" or a puncture resistant container for throwing away needles after you are done with them. The container should be made from hard plastic or metal. Make sure it has a lid. You can also put used syringes or empty vials of medicine in the container.

Material Included in Injection Box and Medication Box:

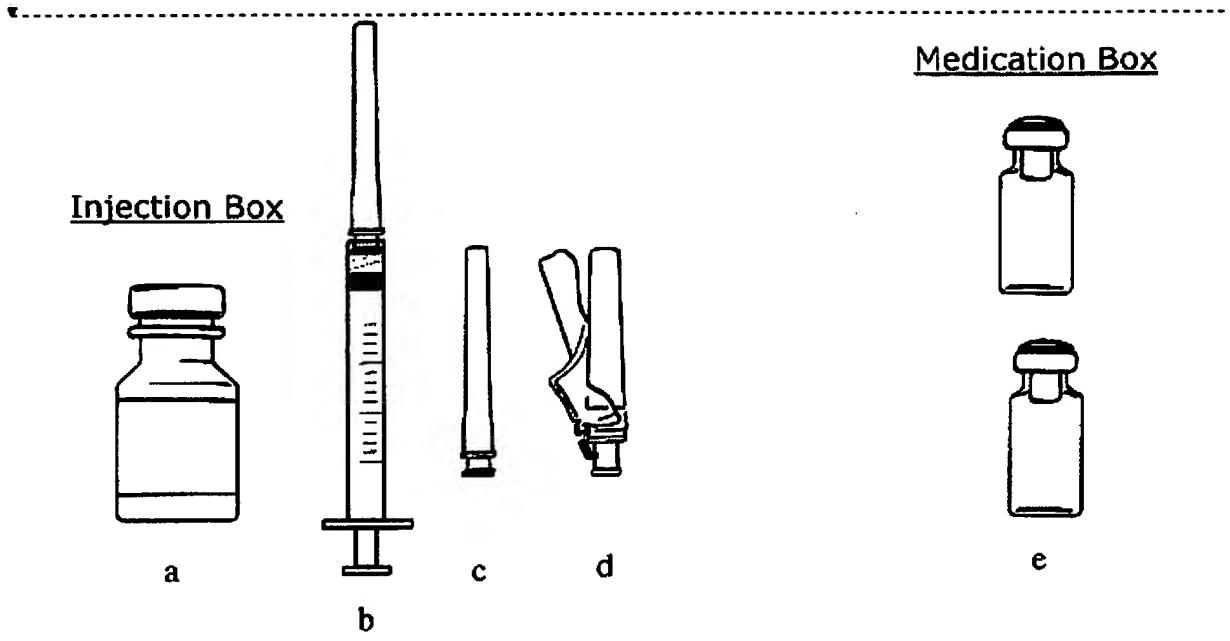


Figure A

You should have the materials as illustrated and lettered in the figure A above:

a) Sterile Water for Injection bottle
b) Syringe with needle already attached (BD 3 mL Syringe)
c) 1½" 18-gauge needle for mixing (BD Blunt Fill Needle)
d) ½" injection needle (BD Eclipse™ Injection Needle)
e) *EGRIFTA*™ powder medication vials (two)

- Take out the following from your Injection Box:
  - A Sterile Water for Injection bottle (Figure A, a)
  - A syringe with needle already attached (Figure A, b)
  - A 1½" 18-gauge needle (Figure A, c)
  - A ½" 27-gauge injection needle (Figure A, d)
- Take two EGRIFTA™ vials (Figure A, e) from the Medication Box. Put the box with the remaining vials back in the refrigerator right away.
- Prepare to use your supplies:
  - Wash your hands with soap and water. Dry your hands with a clean towel.
  - Take off the plastic caps from the vials of EGRIFTA™ and Sterile Water.
  - Clean the rubber stopper on top of the vial(s) with an alcohol swab.

How to mix EGRIFTA™

Step 1: Pick up the syringe with needle attached (Figure A, b), remove the protective cap and insert the needle through the rubber stopper of the bottle of Sterile Water (Figure A, a; see Figure B for illustration). Turn both upside down, and pull back the plunger until the liquid reaches the 2.2 mL mark on the syringe. (See Figure C)

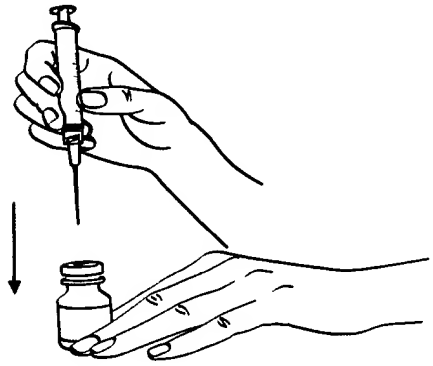


Figure B

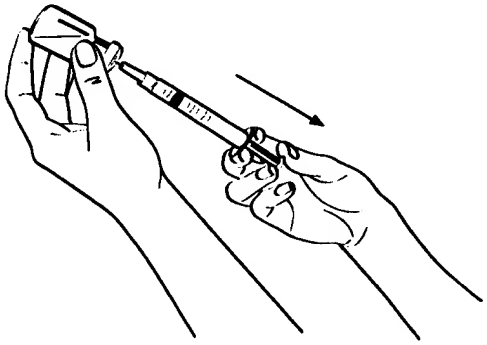


Figure C

Step 2: Take the syringe with needle attached out of the Sterile Water bottle and insert the needle into the EGRIFTA™ vial. Push the plunger in slowly on a slight angle so water goes down the inside wall of the EGRIFTA™ vial instead of directly onto the powder to avoid foaming. (See Figure D)

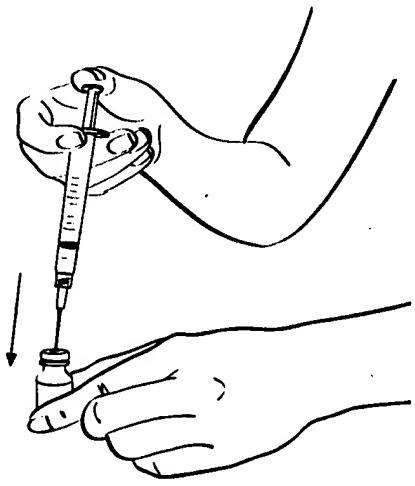


Figure D

Step 3: While keeping the syringe with needle attached in the vial and the vial upright, roll the vial gently in your hands for 30 seconds, until the Sterile Water and EGRIFTA™ powder are mixed well. Do **not** shake the vial. (See Figure E)

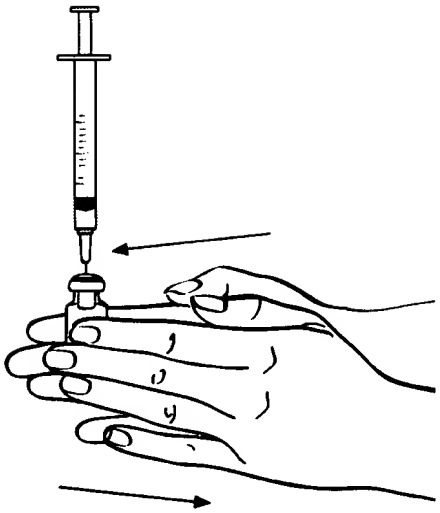


Figure E

Step 4: Still keeping the syringe with needle attached in the vial, turn both until the syringe is straight up. Pull down on the syringe until you see just the tip of the needle going through the rubber stopper, then pull back on the plunger until all the liquid inside the vial goes into the syringe. The level of medicine in the syringe should be around the 2.2 mL syringe mark. (See Figure F)

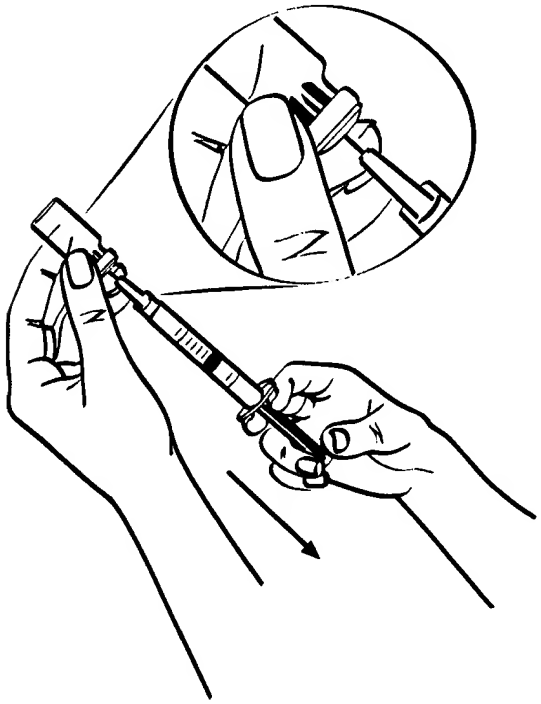


Figure F

Step 5: Take the needle out of the vial. (See Figure G)

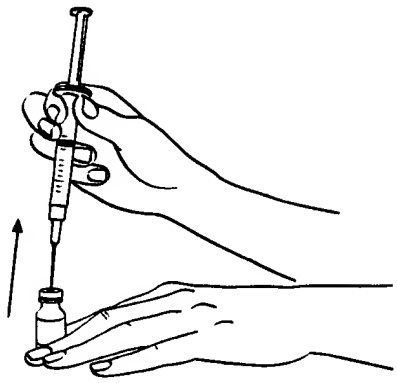


Figure G

Step 6: Place the needle cap on its side against a clean flat surface. Without touching the needle, hold the syringe and slide the needle carefully into the protective cap (See Figure H). Push the cap all the way or until it snaps shut (See Figure I). Do not touch the cap until it covers the needle completely.

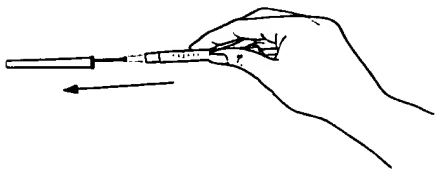


Figure H

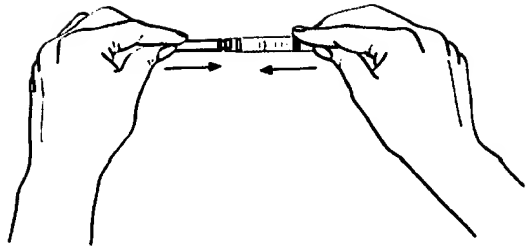


Figure I

Step 7: With the cap on the needle, remove the needle by holding the syringe firmly and twisting the cap counterclockwise (to the left). (See Figure J)

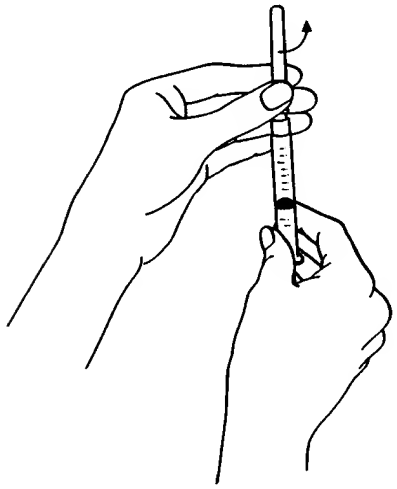


Figure J

Step 8: Place the 1½" 18-gauge mixing needle (Figure A, c), with its protective cap in place, onto the syringe. Twist the cap clockwise (to the right) until it is tight. (See Figure K)

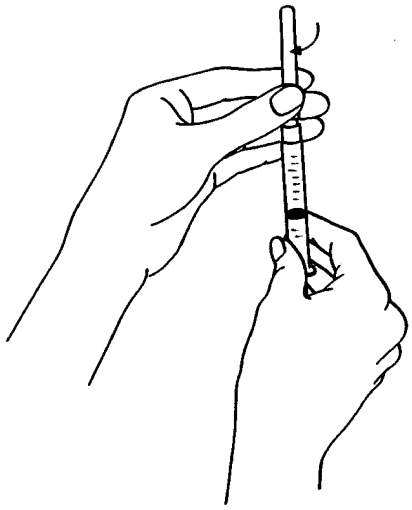


Figure K

Step 9: Remove the protective cap and insert the needle into the second *EGRIFTA*™ vial (Figure A, e). Push the plunger in slowly on a slight angle so that water goes down the inside wall of the EGRIFTA vial instead of directly into the powder to avoid foaming (see Figure L).

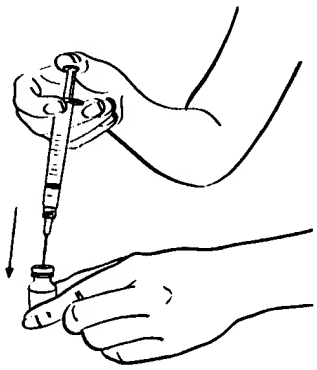


Figure L

Step 10: Keeping the syringe in the vial and the vial upright, roll the vial gently in your hands for 30 seconds, until the water and powder are mixed well. (Do **not** shake the vial.) The solution should look clear and colorless, with no particles in it. (See Figure M)

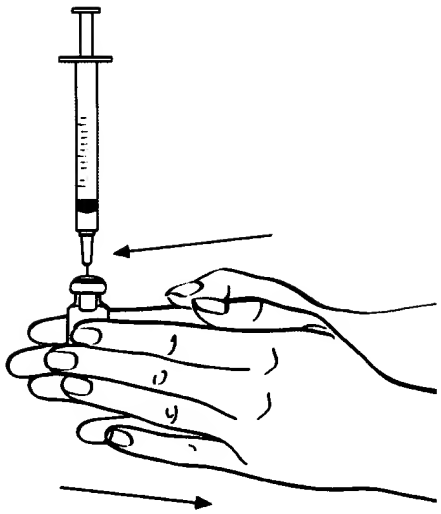


Figure M

Step 11: Still keeping the syringe in the vial, turn both until the syringe is facing upright. Carefully pull down on the syringe until you see just the tip of the needle going through the rubber stopper, then pull back on the plunger until all the liquid inside the vial goes into the syringe. The level of medicine in the syringe should be around the 2.2 mL syringe mark. (See Figure N)

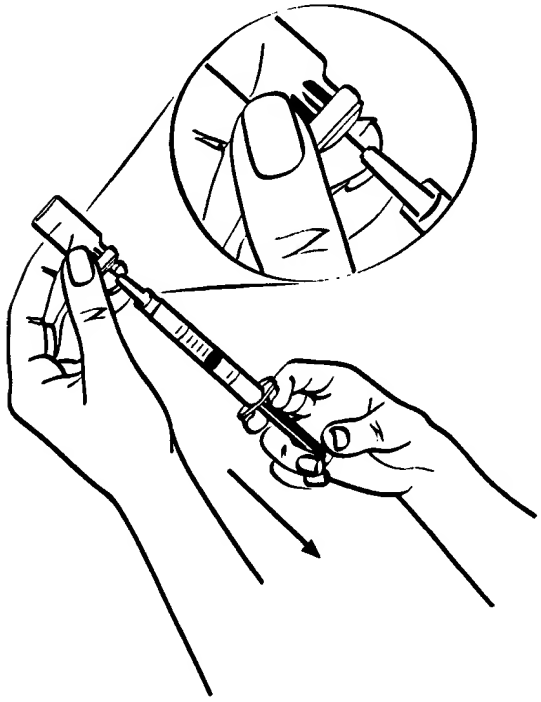


Figure N

Step 12: Carefully take the needle out of the vial. (See Figure O)

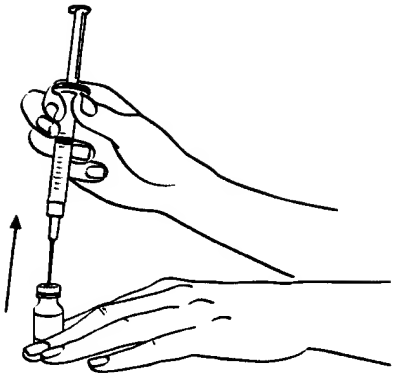


Figure O

Step 13: Place the needle cap on its side against a clean flat surface. Without touching the needle, hold the syringe and slide the needle carefully into the protective cap (See Figure P). Push the cap all the way until it snaps shut (See Figure Q). (Do not touch the cap until it covers the needle completely.)

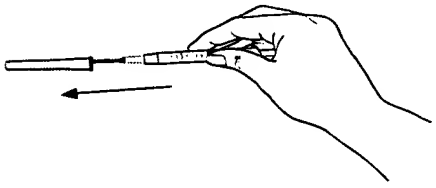


Figure P

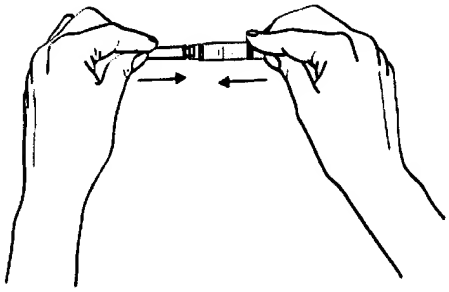


Figure Q

With the needle cap on the needle, remove the mixing needle by holding the syringe firmly and twisting the cap counterclockwise. (See Figure R)

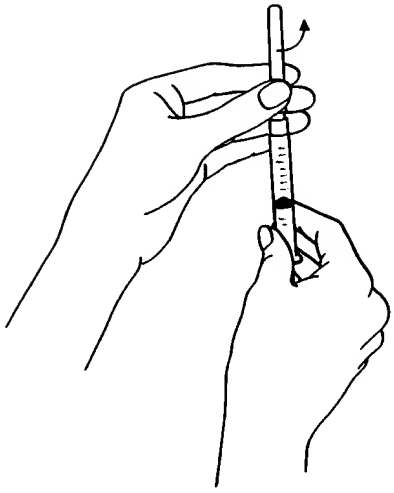


Figure R

Step 14: Place the safety injection needle (Figure A, d), with its protective cap in place, onto the syringe. Hold the syringe firmly and twist the cap clockwise (to the right) until it closes securely. (See Figure S)

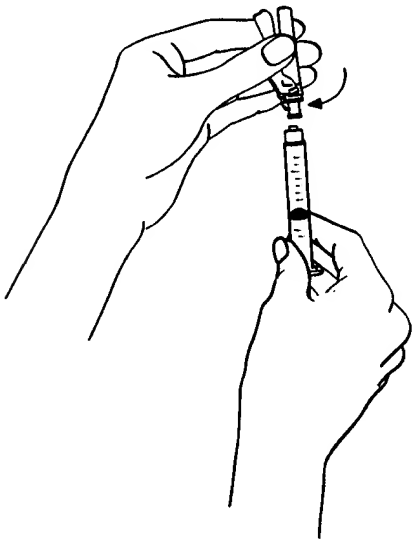


Figure S

Where do I inject EGRIFTA ™?

You should inject EGRIFTA™ into the skin on your stomach (abdomen). (See Figure T)

- Pick an injection site that is below your belly button to the left or right.
- Stay away from any area with scar tissue, bruises, reddening, infection, or irritation.
- Avoid areas with any hard bumps from previous injections.

- Change your injection site from one day to the next. This may help prevent bruising or irritation. You may want to keep a note of the date and location of each daily injection to help you remember.

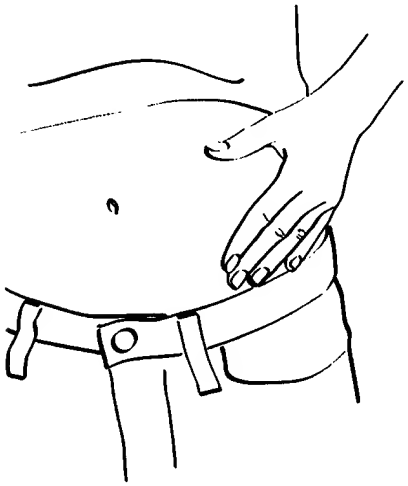


Figure T

How to inject EGRIFTA ™

- Pick up the syringe and pull the cap straight off the injection needle. Do **not** twist it. (See Figure U)

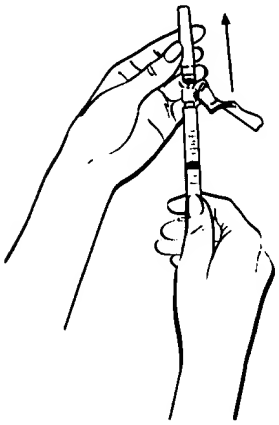


Figure U

- Tap the syringe gently with your finger to force any air bubbles to rise to the top. Press the plunger to push bubbles out. (See Figure V)

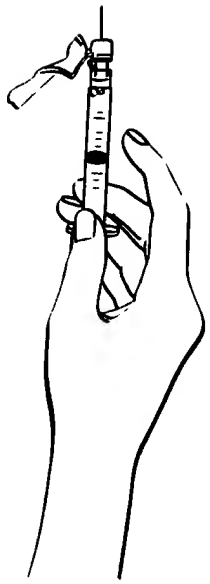


Figure V

- Clean the injection site you have selected with an alcohol swab and let it dry. Hold the syringe in one hand. Use your other hand to hold a cleaned fold of skin for your injection. Hold the skin between your thumb and fingers. (See Figure W)

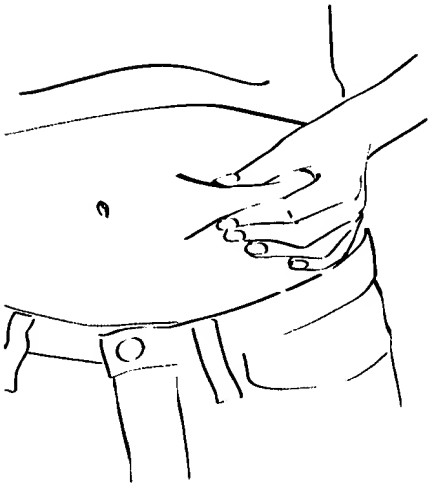


Figure W

- Hold the syringe at a right angle to the skin, like a dart. Push the injection needle into the skin with a quick motion. Most of the needle should go beneath the skin surface. (See Figure X)

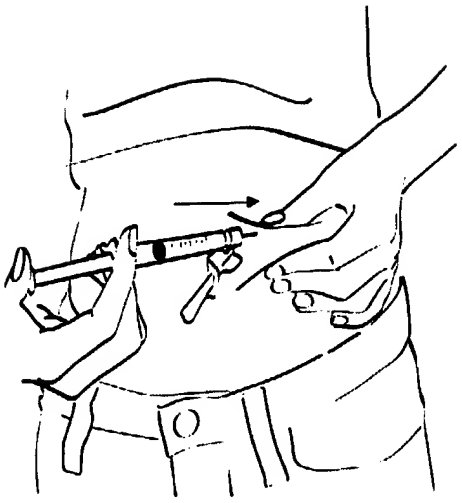


Figure X

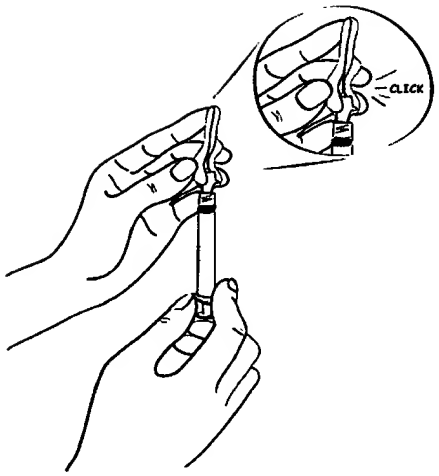
- Remove your hand from the pinched area of skin after the needle goes in. Make sure the needle stays in the skin. (See Figure Y)

Figure Y

- Slowly push the plunger all the way down until all of the medicine in the syringe has been injected under the skin.

- Pull the injection needle out of your skin when the syringe is empty:
  - Be careful to pull it out at the same angle you put it in
  - Flip back the needle shield until it snaps, covering the injection needle completely. Keep pressing until you hear a click, that means the injection needle is protected (Figure Z).

Figure Z



- Use a piece of sterile gauze to rub the injection site clean. If there is bleeding, apply pressure to the injection site with gauze for 30 seconds. If bleeding continues, apply a bandage to the site.

How should I dispose of the used syringes, needles, bottles and vials?

- *If you accidentally prick another person with a used needle, that person should be informed to contact a healthcare provider right away about the accident.*
- Never reuse or recycle needles or syringes.
- Never throw used needles, syringes, or the sharps container into the trash.
- Throw away used syringes, needles, EGRIFTA™ vials and Sterile Water for Injection bottle in a puncture-proof container, sharps container, or a hard container like a coffee can.
- Speak to your pharmacist or other healthcare provider about the proper disposal of the sharps container and all other used materials. There may be local or state laws about how to throw away used needles and syringes.
- Keep the sharps container away from children and pets.

If you have any questions, call your healthcare provider. You can call AXIS Center toll free at 1-877-714-2947 or visit the EGRIFTA™ Web site at www.EGRIFTA.com for more information.

How do I store *EGRIFTA*™?

- EGRIFTA™ has two boxes:
  - Store the Medication Box of EGRIFTA™ vials in the refrigerator between 2°C and 8°C (36°F and 46°F).
  - Store the Injection Box of Sterile Water for Injection, syringes and needles at room temperature between 20°C to 25°C (68°F to 77°F).
- Keep EGRIFTA™ vials away from light.

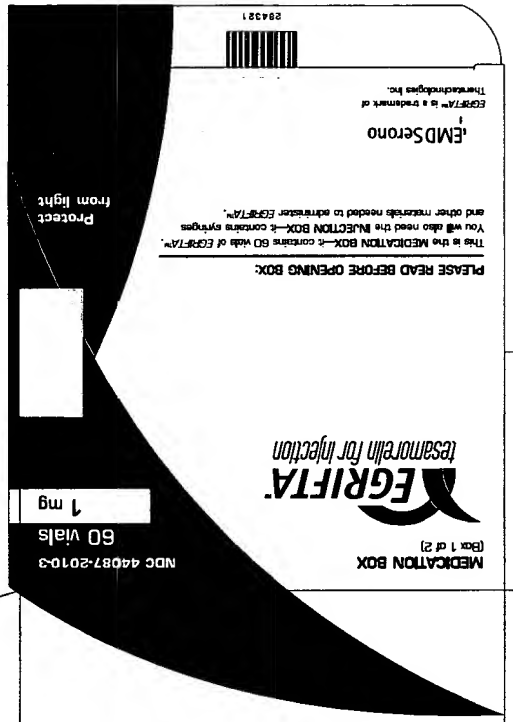
- Do not freeze.
- After mixing, use EGRIFTA™ right away and throw away any unused *EGRIFTA™*. Do not store mixed EGRIFTA™. Also, throw away the used bottle of Sterile Water for Injection
- Do not use EGRIFTA™ after the expiration date printed on the Medication Box and vial labels.

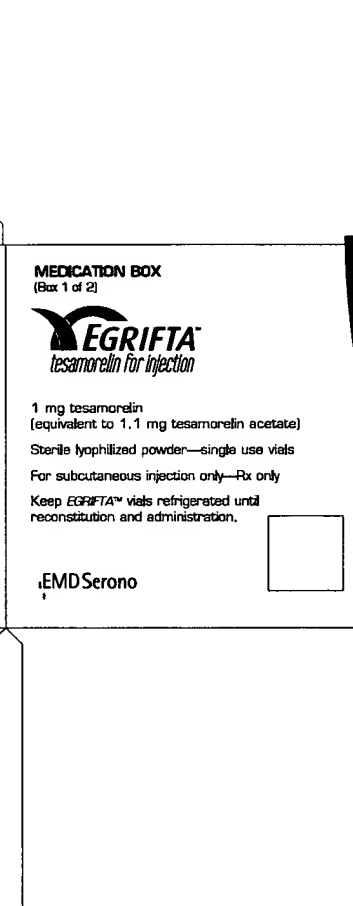
Keep *EGRIFTA*™ and all medicines out of the reach of children.

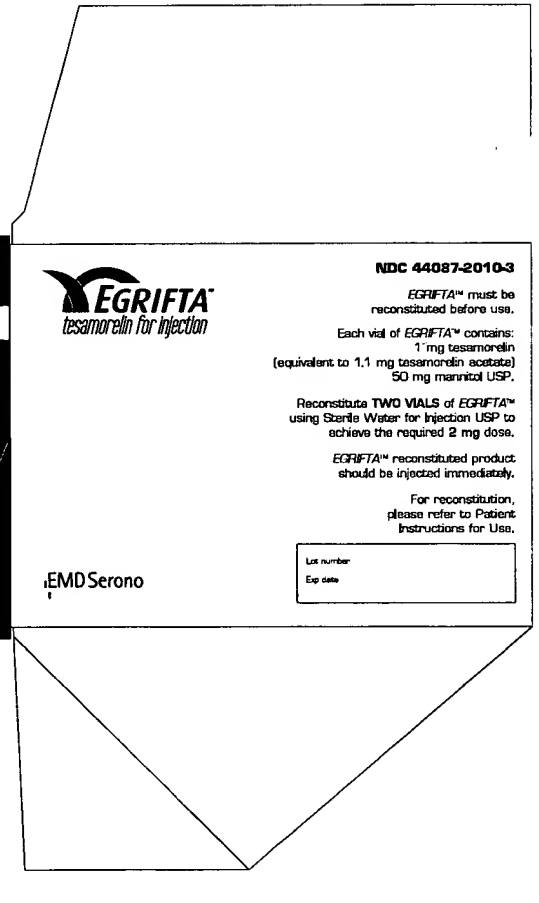
EMD Serono EMD

EGRIFTA™ is a trademark of Theratechnologies Inc.

Distributed by: EMD Serono, Inc., Rockland, MA 02370, USA
Date: 2010-09-27







Reference ID: 2863003

If you notice that some items are missing, or if any item looks damaged, contact AXIS Center toll-free at 1-877-714-2947.

INJECTION BOX (Box 2 of 2)

For reconstitution, please refer to Patient Instructions for Use.

PLEASE READ BEFORE OPENING BOX

This is your INJECTION BOX for *EGRIFTA*™ (tesamorelin for injection). This box contains sterile syringes, Sterile Water for Injection USP, and materials needed for injecting *EGRIFTA*™. Please note this INJECTION BOX does NOT contain your *EGRIFTA*™ medication.

Before removing contents, make sure you also have the *EGRIFTA*™ MEDICATION BOX on hand.

Contents of INJECTION BOX:

a) 30 10-mL bottles of Sterile Water for Injection
b) 30 sterile 3-mL syringes with needle already attached (BD 3 mL Syringe)
c) 30 individual 1¼" 18-gauge sterile needles (BD Blunt Fill Needle)
d) 30 individual ½" 27-gauge sterile injection needles (BD Eclipse™ Injection Needle)
Patient Instructions for Use

Made in USA
Distributed by EMD Serono, Inc., Rockland, MA 02370 USA

EMD Serono

EGRIFTA™ is a trademark of TheraTechnologies Inc.

CA4558

PMS 391 Background 10%
PROCESS CYAN
PMS 391 C13 M0 Y100 K33
PROCESS MAGENTA
PMS 526 C84 M100 Y12 K0
PROCESS YELLOW
BLACK

Reference ID: 2863003

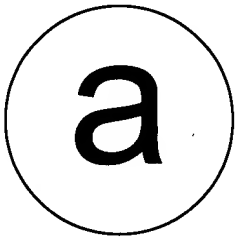
Injection Box Identification Sticker	
10-mL bottles of Sterile Water for Injection	To be affixed on top of 30-pack tray

Stickers description:

- Round 15/16" diameter
- White backing paper
- Gloss finish

Letters:

- lower case
- black ink
- font Arial
- font size: 72



Injection Box Identification Sticker	
Sterile 3-mL syringes with needle already attached (BD 3 mL Syringe)	To be affixed on the top lid of the box of 30

Sticker description:

- Round 15/16" diameter
- White backing paper
- Gloss finish

Letters:

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- font Arial
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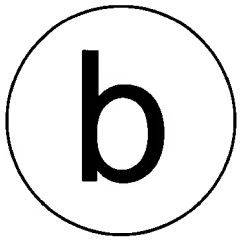

Injection Box Identification Sticker	
Individual 1½" 18-gauge sterile needles (BD Blunt Fill Needle)	To be affixed on the top lid of the box of 30

Stickers description:

- Round 15/16" diameter
- White backing paper
- Gloss finish

Letters:

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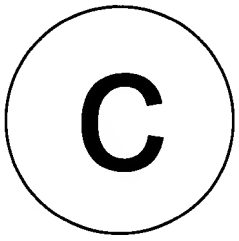
- font size: 72



Injection Box Identification Sticker	
Individual ½" 27-gauge sterile injection needles (BD Eclipse™ Injection Needle)	To be affixed on the top lid of the box of 30

Stickers description:

- Round 15/16" diameter
- White backing paper
- Gloss finish

Letters:

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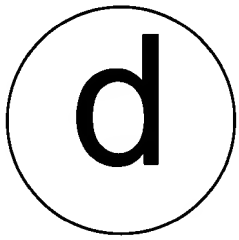

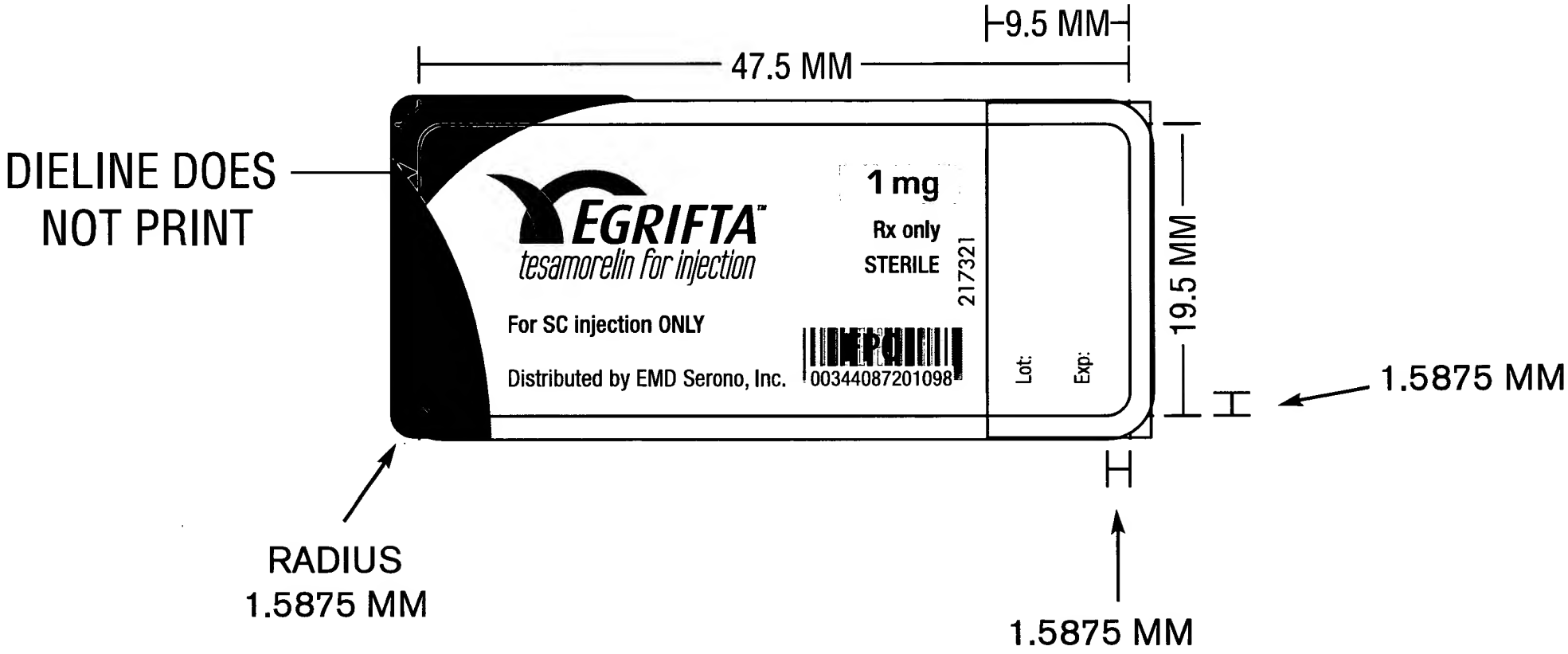
9.5 MM
47.5 MM
DIELINE DOES NOT PRINT
EGRIFTA™
tesamorelin for injection
1 mg
Rx only
STERILE
217321
For SC injection ONLY
Distributed by EMD Serono, Inc.
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Exp:
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RADIUS 1.5875 MM
1.5875 MM

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Document Name: QRL-2906v1.qxp

PMS Black

APPROVED
By Kim Andersen at 11:22 am, Mar 03, 2010

10 mL Single-dose

Sterile Water for Inj., USP

℞ only

Hospira

NDC 0409-4887-34

FOR DRUG DILUENT USE. Contains no antimicrobial or other added substance. Sterile, nonpyrogenic. Do not give intravenously unless rendered nearly isotonic.

RL-2906

Hospira Inc., Lake Forest, IL 60045 USA

Reference ID: 2863003

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PMS Black

APPROVED
By Kim Andersen at 11:21 am, Mar 03, 2010

10 mL Single-dose ℞ only 30 Units/NDC 0409-4887-34

Sterile Water for Injection, USP

FOR DRUG DILUENT USE

Hospira

Hospira, Inc., Lake Forest, IL 60045 USA

USE ASEPTIC TECHNIQUE
Remove cover from Fliptop vial and cleanse stopper with antiseptic.
With Sterile Syringe and Needle:
1. Aspirate desired portion of vial contents and add to suitable container.
2. Discard any remaining fluid in Fliptop vial.
Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

(01) 1 030409 488734 7

Contains no antimicrobial or other added substance.
Sterile, nonpyrogenic.
Use only if clear and seal is intact and undamaged.
Do not give intravenously unless rendered nearly isotonic.
Use promptly; discard unused portion.

Printed in USA

CA-2153

10 mL Single-dose ℞ only 30 Units/NDC 0409-4887-34

Sterile Water for Injection, USP

FOR DRUG DILUENT USE

Hospira, Inc., Lake Forest, IL 60045 USA

Hospira

Reference ID: 2863003

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/s/

CURTIS J ROSEBRAUGH
11/10/2010

US005861379A

United States Patent [19]

Ibea et al.

[11] Patent Number: 5,861,379

[45] Date of Patent: Jan. 19, 1999

[54] **CHIMERIC FATTY BODY-PRO-GRF ANALOGS WITH INCREASED BIOLOGICAL POTENCY**

[75] Inventors: **Michel Ibea**; **Thierry Abribat**; **Paul Brazeau**, all of Montréal, Canada

[73] Assignee: **Theratechnologies Inc.**, Montreal, Canada

[21] Appl. No.: **702,114**

[22] Filed: **Aug. 23, 1996**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 651,645, May 22, 1996, abandoned, and Ser. No. 453,067, May 26, 1995, abandoned.

[51] **Int. Cl.**[6] **A61K 38/25**; C07K 14/60

[52] **U.S. Cl.** **514/12**; 530/324; 530/345; 530/399; 530/402; 930/120

[58] **Field of Search** 530/324, 345, 530/399, 402; 514/12; 930/120

[56] **References Cited**

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Coy et al., "Differential Effects of N–Terminal Modification on the Biological Potencies of Growth Hormone Releaseing Factor Analogues with Varying Chain Lengths", J. Med. Chem., vol. 30, pp. 219–222, 1987.

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Coy et al, J. Med. Chem., vol. 30, pp. 219–222 (1987).

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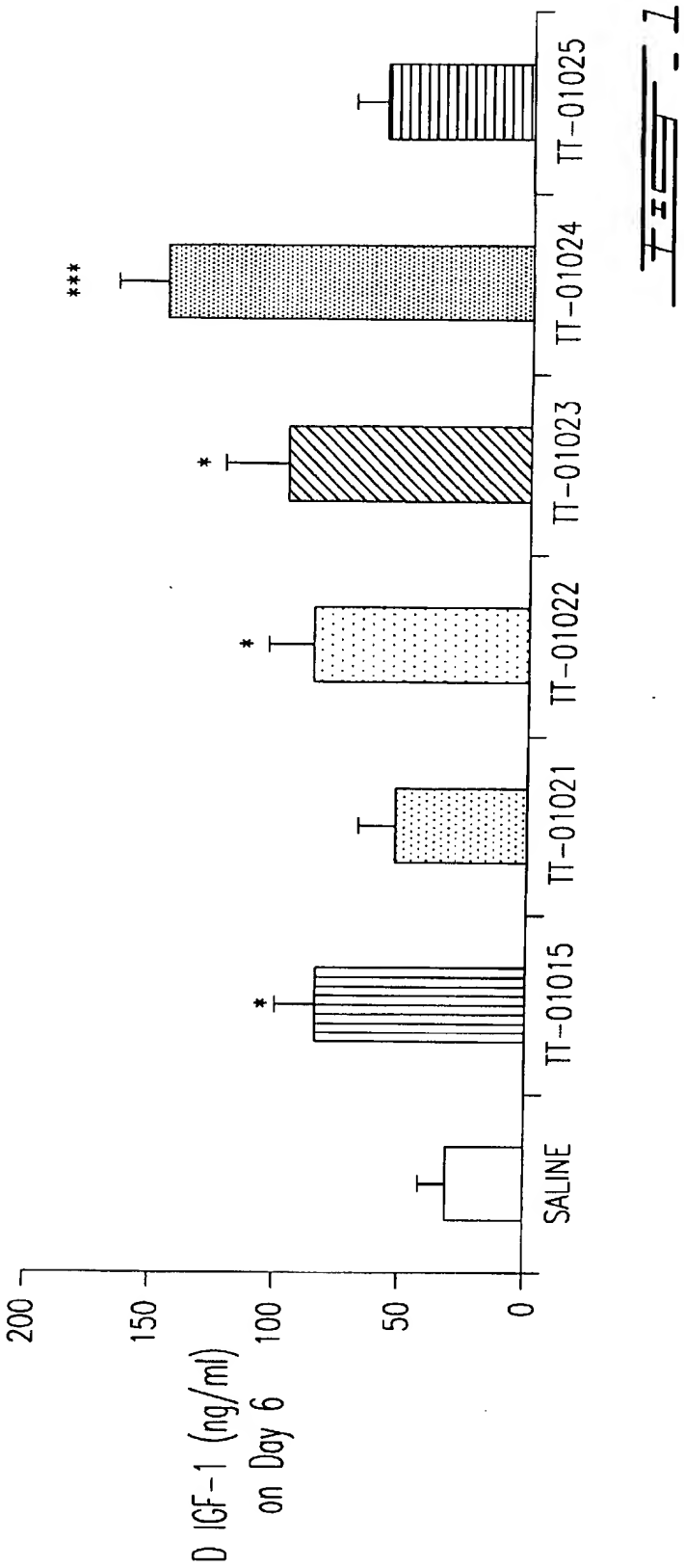
Primary Examiner—Cecilia J. Tsang
Assistant Examiner—Anish Gupta
Attorney, Agent, or Firm—Evenson, McKeown, Edwards & Lenahan, P.L.L.C.

[57] **ABSTRACT**

The present invention relates to chimeric fatty body-pro-GRF analogs with increased biological potency, their application as anabolic agents and in the diagnosis and treatment of growth hormone deficiencies. The chimeric fatty body-pro-GRF analogs include an hydrophobic moiety (tail), and can be prepared, either by anchoring one or several hydrophobic tails to the GRF, or by substituting one or several amino-acids by a pseudomicellar residue in the chemical synthesis of GRF. The GRF analogs of the present invention are biodegradable, non-immunogenic and exhibit an improved anabolic potency with a reduced dosage and prolonged activity.

17 Claims, 5 Drawing Sheets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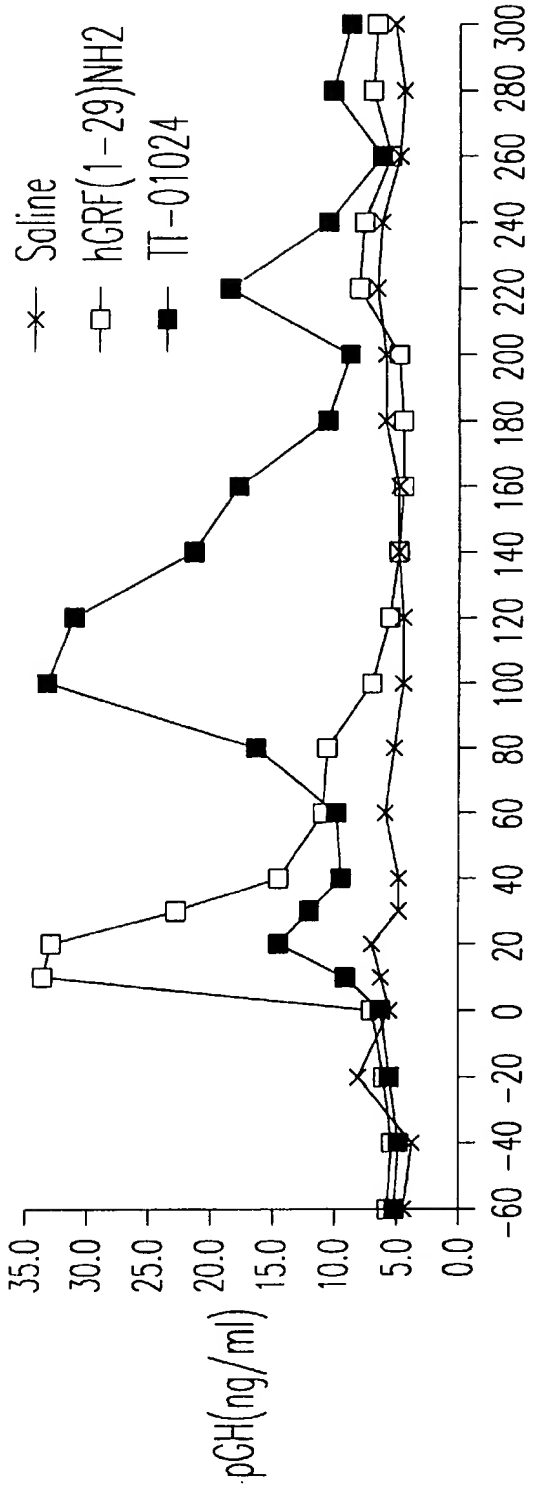
200
150
100
50
0
SALINE
TT-01015
TT-01021
TT-01022
TT-01023
TT-01024
TT-01025
*
*
*
*
***

Fig. 1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TT-01024
pGH(ng/ml)
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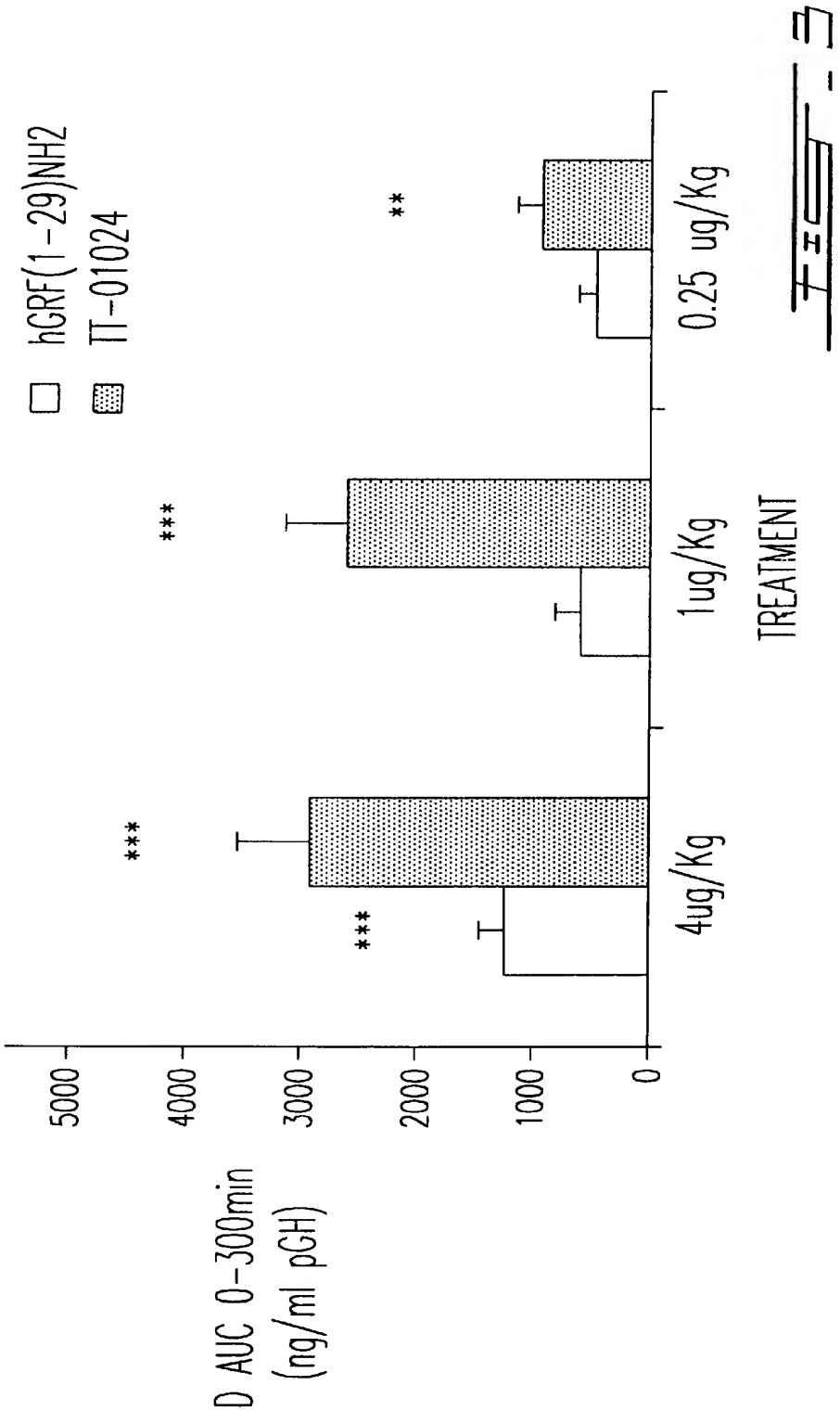
30.0
25.0
20.0
15.0
10.0
5.0
0.0
-60 -40 -20 0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300
Minutes

Fig. 2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TT-01024
D AUC 0-300min
(ng/ml pGH)
5000
4000
3000
2000
1000
0
***
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1ug/Kg
0.25 ug/Kg
TREATMENT

Fig. 3

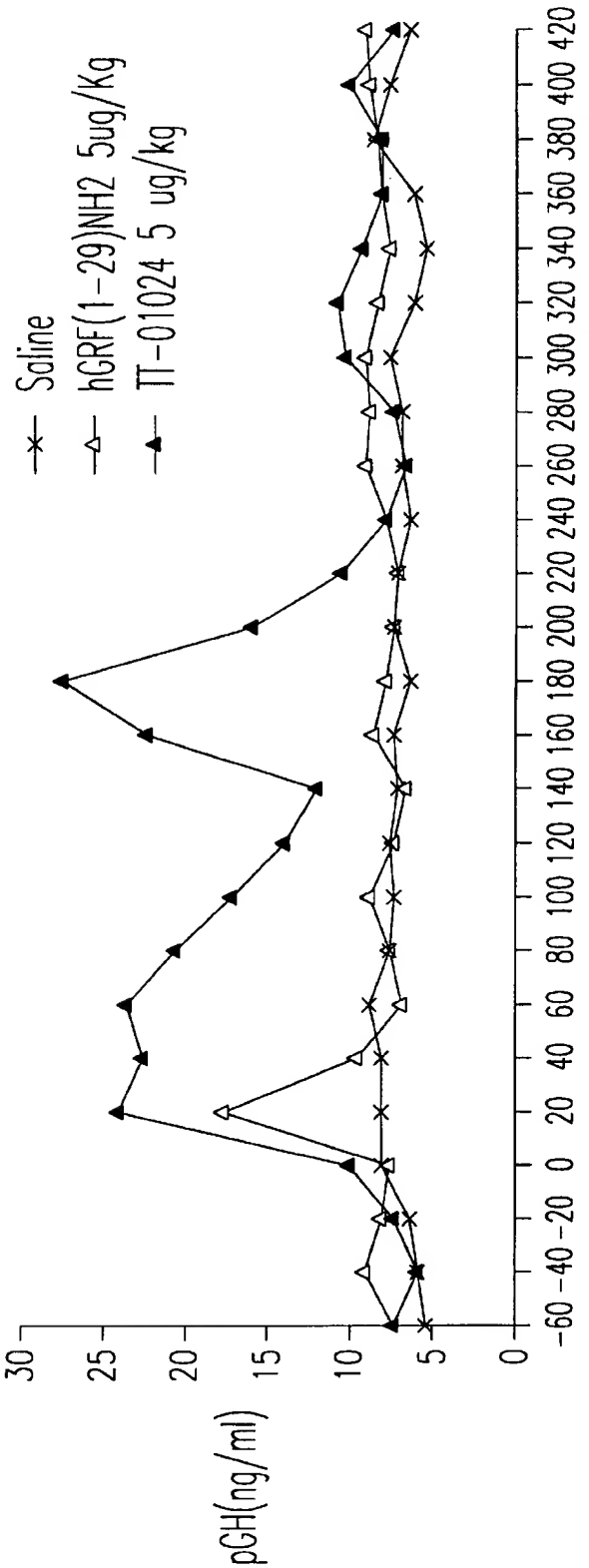
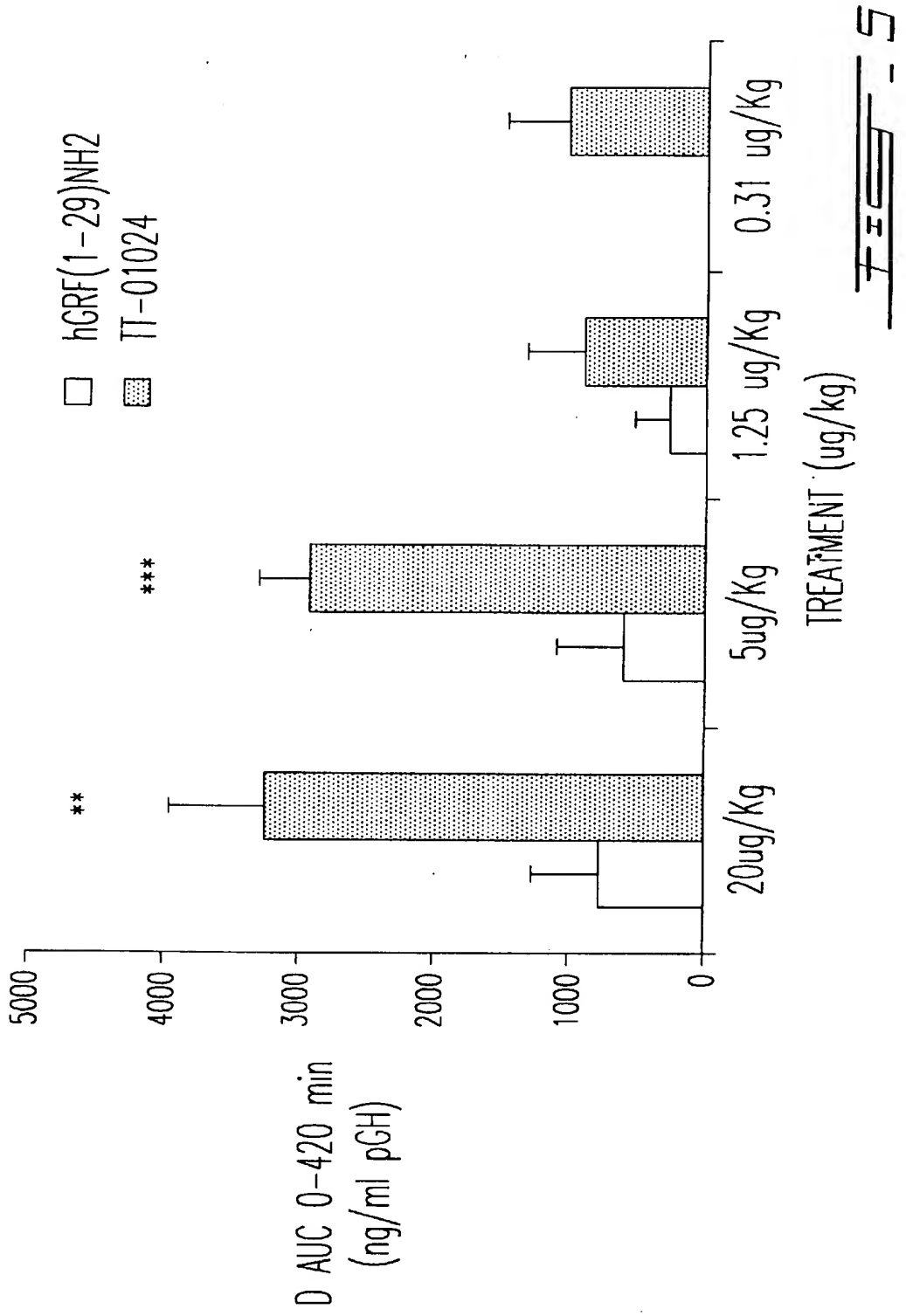

Saline
hGRF(1-29)NH2 5ug/Kg
TT-01024 5 ug/kg
pGH(ng/ml)
30
25
20
15
10
5
0
-60 -40 -20 0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420
Minutes

Fig - 4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TT-01024
**
***
D AUC 0-420 min (ng/ml pGH)
5000
4000
3000
2000
1000
0
20ug/Kg
5ug/Kg
1.25 ug/Kg
0.31 ug/Kg
TREATMENT (ug/kg)

FIG - 5

CHIMERIC FATTY BODY-PRO-GRF ANALOGS WITH INCREASED BIOLOGICAL POTENCY

RELATED APPLICATION

This application is a continuation-in-part of application Ser. No. 08/651,645 filed on May 22, 1996, now abandoned, and is a continuation-in-part of application Ser. No. 08/453,067 filed on May 26, 1995 and which is abandoned.

BACKGROUND OF THE INVENTION

(a) Field of the Invention

The invention relates to chimeric fatty body-pro-GRF analogs with increased biological potency and prolonged activity, their application as anabolic agents and treatment of growth hormone deficiencies.

(b) Description of Prior Art

Growth hormone (GH) or somatotropin, secreted by the pituitary gland constitute a family of hormones which biological activity is fundamental for the linear growth of a young organism but also for the maintenance of the integrity at its adult state. GH acts directly or indirectly on the peripheral organs by stimulating the synthesis of growth factors (insulin-like growth factor-I or IGF-I) or of their receptors (epidermal growth factor or EGF). The direct action of GH is of the type referred to as anti-insulinic, which favors the lipolysis at the level of adipose tissues. Through its action on IGF-I (somatomedin C) synthesis and secretion, GH stimulate the growth of the cartilage and the bones (structural growth), the protein synthesis and the cellular proliferation in multiple peripheral organs, including muscles and the skin. Through its biological activity, GH participates within adults at the maintenance of a protein anabolism state, and plays a primary role in the tissue regeneration phenomenon after a trauma.

The decrease of GH secretion with the age, demonstrated in humans and animals, favors a metabolic shift towards catabolism which initiates or participate to the aging of an organism. The loss in muscle mass, the accumulation of adipose tissues, the bone demineralization, the loss of tissue regeneration capacity after an injury, which are observed in elderly, correlate with the decrease in the secretion of GH.

GH is thus a physiological anabolic agent absolutely necessary for the linear growth of children and which controls the protein metabolism in adults.

The secretion of GH by the pituitary gland is principally controlled by two hypothalamic peptides, somatostatin and growth hormone-releasing factor (GRF). Somatostatin inhibits its secretion, whereas GRF stimulates it.

The human GH has been produced by genetic engineering for about ten years. Until recently most of the uses of GH were concerned with growth delay in children and now the uses of GH in adults are studied. The pharmacological uses of GH and GRF may be classified in the following three major categories.

Children growth

Treatments with recombinant human growth hormone have been shown to stimulate growth in children with pituitary dwarfism, renal insufficiencies, Turner's syndrome and short stature. Recombinant human GH is presently commercialized as an "orphan drug" in Europe and in the United States for children's growth retardation caused by a GH deficiency and for children's renal insufficiencies. The other uses are under clinical trial investigation.

Long term treatment for adults and elderly patients

A decrease in GH secretion causes changes in body composition during aging. Preliminary studies of one-year treatment with recombinant human GH reported an increase in the muscle mass and in the thickness of skin, a decrease in fat mass with a slight increase in bone density in a population of aged patients. With respect to osteoporosis, recent studies suggest that recombinant human GH does not increase bone mineralization but it is suggested that it may prevent bone demineralization in post-menopausal women. Further studies are currently underway to demonstrate this theory.

Short term treatment in adults and elderly patients

In preclinical and clinical studies, growth hormone has been shown to stimulate protein anabolism and healing in cases of burn, AIDS and cancer, in wound and bone healing.

GH and GRF are also intended for veterinary pharmacological uses. Both GH and GRF stimulate growth in pigs during its fattening period by favoring the deposition of muscle tissues instead of adipose tissues and increase milk production in cows, and this without any undesired side effects which would endanger the health of the animals and without any residue in the meat or milk being produced. The bovine somatotropin (BST) is presently commercialized in the United States.

Most of the clinical studies presently undertaken were conducted with recombinant GH. The GRF is considered as a second generation product destined to replace in the near future the uses of GH in most instances. Accordingly, the use of GRF presents a number of advantages over the use of GH per se.

Physiological advantages

Growth hormone (GH) is secreted by the pituitary gland in a pulse fashion, since this rhythm of secretion is crucial for an optimal biological activity. The administration of GH to correspond to its natural mode of secretion is difficult to achieve. When GRF is administered in a continuous fashion as a slow releasing preparation or as an infusion, it increases GH secretion while respecting its pulsatility.

The recombinant GH which is presently commercialized is the 22 kDa form whereas GRF induces the synthesis and secretion from the pituitary gland of all the chemical isomers of GH which participate in a wider range of biological activities.

A treatment with GH results in a decreased capacity of the pituitary gland to secrete endogenous growth hormone, and the GH response to GRF is diminished after such a treatment. On the contrary, a treatment with GRF does not present this disadvantages, its trophic action on the pituitary gland increases this gland secreting capacity in normal animals and in patients with somatotroph insufficiency.

Economical advantages

The production of GH by genetic engineering is very expensive for clinical use. In particular, there are risks of contamination of these commercial preparation with material from the bacterial strain used. These bacterial contaminants may be pyrogens or may result in immunogenic reactions in patients. The purification of the recombinant product is effected by following a plurality of successive chromatography steps. The drastic purity criteria causes multiple quality control steps.

The synthesis of GRF is of chemical nature. The synthesis effected in a solid phase and its purification is carried out in a single step using high performance liquid chromatography (HPLC). Also the quantity of GRF to be administered is much less than the quantity of GH for the same resulting biological activity.

Even with all these advantages, GRF is still not commercialized to date as a therapeutic agent mainly because of its

chemical instability. The human GRF is a peptide of 44 amino acids of the following sequence:

Tyr Ala Asp Ala Ile Phe Thr Asn Ser Tyr Arg Lys Val Leu Gly Gln
1 5 10 15

Leu Ser Ala Arg Lys Leu Leu Gln Asp Ile Met Ser Arg Gln Gln Gly
20 25 30

Glu Ser Asn Gln Glu Arg Gly Ala Arg Ala Arg Leu—NH_2
35 40 (SEQ ID NO: 1).

The minimum active core is hGRF (1-29)NH_2

Tyr Ala Asp Ala Ile Phe Thr Asn Ser Tyr Arg Lys Val Leu Gly Gln
1 5 10 15

Leu Ser Ala Arg Lys Leu Leu Gln Asp Ile Met Ser Arg
20 25 (SEQ ID NO: 2).

As for many peptides, hGRF (1–29)NH_2 is rapidly degraded in a serum medium and its metabolites have no residual biological activity. It has been well established that the action of enzymes, namely that of dipeptidylaminopeptidase type IV, in a blood medium results in the hydrolysis of the peptide bond Ala^2-Asp^3 of GRF. This hydrolysis results in a multitude of negative consequences which was the subject of many studies reported in the literature. Essentially, this hydrolysis leads to the formation of truncated peptides of specific activity reduced to less than 1/1000 of the biological activity.

Clinical studies with children and adults have confirmed that natural hGRF (1–44)NH_2 or the active fragment hGRF (1–29)NH_2 are not potent enough to produce equal effects corresponding to those of recombinant GH.

Many GRF analogs have been described, but they all present the disadvantages of being modified GRF having a different amino acid sequence or having synthetic amino acids (D series) added. These GRF analogs are potentially immunogenic and their administration to human may cause immunotoxicity problems and potential side effects.

It is well known that the anchoring of hydrophobic groups, such as -NEt_2 at the C-terminal of a peptidic sequence can result in a significantly increased specific activity. In terms of hydrophobicity, these results are contradicted by a fare number recent works such as those of Muranichi (S. Muranichi et al., 1991, *Pharm. Res.*, 8:649–652) which stress the inefficacy of the lauroyl group as an hydrophobic group used in the synthesis of small peptides analogs. Hence, the contradictory investigations of the prior art failed to address the issue of finding a more potent GRF analog using hydrophobic residues.

Gaudreau et al. (P. Gaudreau et al., 1992, *J. Med. Chem.*, 35(10),:1864–1869) describe the affinity of acetyl-, 6-aminohexanoyl-, and 8-aminooctanoyl-GRF(1–29)NH_2 with the rat pituitary receptor. In this report, none of the fatty acid-GRF compounds tested exhibited a higher affinity than hGRF(1–29)NH_2 itself, and the authors concluded that ". . . modifications to increase the hydrophobic character at the N-terminus of hGRF(1–29)NH_2 do not constitute a suitable approach to increase receptor affinity.".

Coy et al. (D. H. Cow et al., 1987, *J. Med. Chem.*, 30:219–222) describe an acetyl-GRF peptide with an increased biological activity on a rat model, more particularly on a rat anesthetized with sodium pentobarbital. The in vitro GH response by cultured rat pituitary cells was also analyzed. However, these authors did not synthesize and test fatty acid-GRF analogs with a carbon chain longer than 2 (acetyl) added at the N-terminus region of the GRF.

Up to now, most of the GRF analogs described (including those of Gaudreau et al. and those of Coy et al.) have been tested in rat models, either in vitro or in vivo. Since human and rat GRF(1–29)NH_2 are markedly different, the structure-activity relationships of GRF is different in both species. Therefore, it is not possible to extrapolate results obtained in rats to human.

Accordingly, it is necessary to design GRF analogs with improved anabolic potency and having a prolonged activity. This increased potency could result from a resistance to serum degradation and/or from hyperagonistic properties.

It would be highly desirable to be provided with GRF analogs with increased anabolic potency, while remaining biodegradable and structurally closed to natural GRF, in order to prevent immune reactions when chronically injected in humans and animals.

SUMMARY OF THE INVENTION

One aim of the present invention is to provide new biodegradable and non-immunogenic pro-GRF analogs with improved biological potency and prolonged activity.

Another aim of the present invention is to provide pro-GRF analogs with increased anabolic potency and prolonged activity, i.e. capable to substantially elevate insulin-like growth factor I (IGF-I) levels when chronically administered in human and animals.

Another aim of the present invention is to provide a mean to render any pro-GRF analog more biologically potent and with a prolonged activity.

Another aim of the present invention is to provide for a method of producing active pro-GRF analogs with improved anabolic potency and prolonged activity.

The present invention relates to the preparation of chimeric fatty body-GRF analogs. These chimeric analogs include an hydrophobic moiety (tail), and can be prepared, either by anchoring one or several hydrophobic tails to the GRF, or by substituting one or several amino-acids by a pseudomicellar residue in the chemical synthesis of pro-GRF. The pro-GRF analogs in accordance with the present invention are characterized in that:

a) These analogs possess an enhanced biological activity; specifically, they are able to markedly increase GH and IGF-I blood levels when administered in an animal model closely related to human. This characteristic is particularly advantageous in that it results in a reduced dosage of an hyperactive compound being administered to the patient, thus improving treatment efficacy and reducing treatment costs.

b) Both natural amino acid and hydrophobic metabolisable substances, such as fatty acids, are used for the chemical synthesis of the pro-GRF analogs. Such a use of natural substances entirely metabolisable is intended to prevent the potential secondary effects, namely in cases of multiple administrations.

c) They present a high biological activity at infinitely small dosages.

d) They remain active for a prolonged period of time, with a high biological activity.

The use of fatty bodies in accordance with the present invention results in pro-GRF analogs which overcome all the drawbacks of the prior art. The pro-GRF analogs of the present invention are biodegradable, non-immunogenic and exhibit an improved anabolic potency with a reduced dosage and have a prolonged activity. Furthermore, the present invention deals with GRF and any of its analogs, truncated or substituted.

Unexpectedly, the results of the present invention showed that N-hexanoyl-, but not N-butyryl- or N-octanoyl-GRF (1–29)NH_2, statistically increased IGF-I levels when chronically administered in growing pigs. These results indicate that the addition of a C4 or a C8 chain at the N-terminus region of GRF yielded compounds with a poor biological activity when compared to the N-hexanoyl-GRF (C6-GRF). Therefore, the present invention teaches that the optimal length of the carbon chain to anchor to GRF to increase its bioactivity is C5 to C7. This result was unexpected based on the studies published by Coy et al., that demonstrated that the N-acetylation of GRF (addition of a C2 chain) increased its bioactivity in rats, and that did not document the activity of compounds with a carbon chain longer than C2.

According to the method of the present invention, these analogs can be produced either by anchoring one or several hydrophobic tails at the N- or C-terminal portion of GRF or its analogs, or by incorporating one or several pseudomicellar residues at any step of the chemical synthesis of GRF or its analogs. After cleavage and purification, the resulting modified peptide exhibits an enhanced biological activity when administered at very low dosage.

In accordance with the present invention, there is provided a chimeric fatty body-pro-GRF analog with increased biological potency, of the following general formula:

A1-A2-Asp-Ala-Ile-Phe-Thr-A8-Ser-Tyr-Arg-Lys-Val-Leu-A15-Gln-Leu-A18-Ala-Arg-Lys-Leu-Leu-A24-Asp-Ile-A27-A28-Arg-A30-R_0

wherein,

A1 is Tyr or His;

A2 is Val or Ala;

A8 is Asn or Ser;

A15 is Ala or Gly;

A18 is Ser or Thr;

A24 is Gln or His;

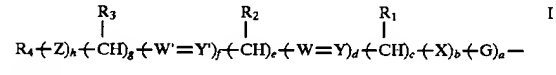
A27 is Met, Ile or Nle;

A28 is Ser or Asp;

A30 is any amino acid sequence of 1 to 15 residues;

R_0 is NH_2;

wherein A1 is N- or O-anchored by a hydrophobic tail of the following general formula I:



I

wherein,

G is a carbonyl, a phosphonyl, a sulfuryl or a sulfinyl group;

X is a oxygen atom, sulfur atom or an amino group (NH);

(W=Y) represents cis or trans ($CH=CR_5$);

(W'=Y') represents cis or trans ($CH=CR_6$);

Z is an oxygen or a sulfur atom;

R_1, R_2 and R_3, independently, are selected from a hydroxyl group, a hydrogen atom, and a linear or branched C_1–C_6 alkyl group;

R_4 is an hydroxyl group, a hydrogen atom or a linear or branched C_5–C_9 alkyl group;

R_5 and R_6, independently, are a hydrogen atom or a linear or branched C_1–C_4 alkyl group;

a is 0 or 1;

b is 0 or 1;

c is 0 to 8;

d is 0 or 1;

e is 0 to 8;

f is 0 or 1;

g is 0 to 8;

h is 0 to 1;

wherein the sum of a, b, c, d, e, f, g and h is such that the hydrophobic tail of formula I has a linear main chain of between 5 and 8 atoms (C, O and/or S).

The preferred chimeric fatty body-pro-GRF analog of the present invention is selected from the group consisting of:

a) wherein A1 is Tyr or His N-alpha anchored by hydrophobic tail of formula I, wherein both a and b=1; each of d, f and h=0; G=carbonyl; X=oxygen atom; R_1, R_2, R_3, R_4=hydrogen atom and the sum c+e+g=3, 4, 5 or 6;

b) wherein A1 is Tyr or His N-alpha anchored by hydrophobic tail of formula I, wherein a=1; each of b, d, f and h=0; G=carbonyl; R_1, R_2, R_3 and R_4=hydroxyl group and the sum c+e+g=4, 5, 6 or 7;

c) wherein A1 is Tyr or His N-alpha anchored by hydrophobic tail of formula I, wherein a=1; each of b and h=0; the sum d+f=1; G=carbonyl; R_1, R_2, R_3 and R_4=hydrogen atom and the sum c+e+g=2, 3, 4 or 5;

d) the compound of c) above wherein c is 0;

e) the compound of d) above wherein A30 is Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu;

f) the compound of e) above wherein R_0 is NH_2;

g) the compound of f) above which is cisCH_3—CH_2—CH=CH—CH_2—CO-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu-NH_2 or transCH_3—CH_2—CH=CH—CH_2—CO-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu-NH_2;

h) wherein A1 is Tyr or His N-alpha anchored by hydrophobic tail of formula I, wherein a=1; each of b and h=0; the sum d+f=2; G=carbonyl; R_1, R_2, R_3 and R_4=hydrogen atom and the sum c+e+g=0, 1, 2 or 3; and

i) wherein A1 is Tyr or His N-alpha anchored by hydrophobic tail of formula I, wherein a=1; each of b, h, d and f=0; G=carbonyl; R_1, R_2, R_3 and R_4=hydrogen atom; and the sum c+e+g=4, 5, 6 or 7.

For the purpose of the present invention, the term "hydrophobic tail" or "Ht" is intended to mean any functionalized fatty body, such as fatty acids, fatty amines, fatty alcohols, cholesterol derivatives, etc. The term "pseudomicellar residue" or "Pr" is intended to mean any α amino acid with side chain designed so that the residue may form or adopt a micellar structure in its switterionic form.

In accordance with the present invention, there is provided a pharmaceutical formulation for inducing growth hormone release which comprises as an active ingredient a GRF analog of the present invention in association with a pharmaceutically acceptable carrier, excipient or diluent.

In accordance with the present invention, there is provided a method of increasing the level of growth hormone in a patient which comprises administering to said patient an effective amount of a GRF analog of the present invention.

In accordance with the present invention, there is provided a method for the diagnosis of growth hormone deficiencies in patients, which comprises administering to said

patient a GRF analog of the present invention and measuring the growth hormone response.

In accordance with the present invention, there is provided a method for the treatment of pituitary dwarfism or growth retardation in a patient, which comprises administering to said patient an effective amount of a GRF analog of the present invention.

In accordance with the present invention, there is provided a method for the treatment of wound or bone healing in a patient, which comprises administering to said patient an effective amount of a GRF analog of the present invention.

In accordance with the present invention, there is provided a method for the treatment of osteoporosis in a patient, which comprises administering to said patient an effective amount of a GRF analog of the present invention.

In accordance with the present invention, there is provided a method for improving protein anabolism (including protein sparing effect) in human or animal, which comprises administering to said human or animal an effective amount of a GRF analog of the present invention.

In accordance with the present invention, there is provided a method for inducing a lipolytic effect in human or animal inflicted with clinical obesity, which comprises administering to said human or animal an effective amount of a GRF analog of the present invention.

In accordance with the present invention, there is provided a method for the overall upgrading of somatroph function in human or animal, which comprises administering to said human or animal an effective amount of a GRF analog of the present invention.

In the present invention the amino acids are identified by the conventional three-letter abbreviations as indicated below, which are as generally accepted in the peptide art as recommended by the IUPAC-IUB commission in biochemical nomenclature:

Alanine	Ala
Arginine	Arg
Asparagine	Asn
Aspartic Acid	Asp
Cysteine	Cys
Glutamic Acid	Glu
Glycine	Gly
Histidine	His
Leucine	Leu
Lysine	Lys
Methionine	Met
Ornithine	Orn
Phenylalanine	Phe
Proline	Pro
Serine	Ser
Threonine	Thr
Tryptophane	Trp
Tyrosine	Tyr
D-Tyrosine	Tyr
Valine	Val

The term "natural amino acid" means an amino acid which occurs in nature or which is incorporated as an amino acid residue in a naturally occurring peptide. In addition, the abbreviation Nle is intended to mean Norleucine.

Other abbreviations used are:

TFA	Trifluoroacetic acid;
HOBt	1- Hydroxybenzotriazole;
DIC	Diisopropylcarbodiimide;
DMF	Dimethylformamide;
Pip	Piperidine;
DMAP	4-dimethylaminopyridine;
Boc	t-butyloxycarbonyl;
Fmoc	Fluorenylmethyloxycarbonyl;
BOP	Benzotriazo-1-yloxytris (dimethylamino) phos phonium hexafluorophosphate;
Me	Methyl;
HF	Hydrofluoric acid;
NEt3	Triethylamine; and
TEAP	Triethylammonium phosphate (buffer).

All the peptide sequences set out herein are written according to the generally accepted convention whereby the N-terminal amino acid is on the left and the C-terminal amino acid is on the right.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a graph of the effect of subcutaneously injected hGRF(1–29) NH_2 analogs on pig serum IGF-1;

FIG. **2** is a curve of the effect of one intravenous injection of (4 μg/kg) hGRF(1–29) NH_2 and (4 μg/kg) (Hexenoyl trans-3)$_0$ hGRF (1–29) NH_2 (TT-01024)+analog on pig serum GH;

FIG. **3** is a graph showing the effect of various doses of hGRF(1–29)NH_2 vs [hexenoyl trans-3]^0 hGRF(1–29)NH_2 (TT-01024) on the GH area under the curve over 300 minutes following I.V. administration (**P<0.01 and ***P<0.001 when compared to the basal period—-60 to 0 min—);

FIG. **4** is a curve of the effect of one subcutaneous injection of 5 μg/kg hGRF(1–29) NH_2 and (5 μg/kg) (Hexenoyl trans-3)$_0$ hGRF (1–29) NH_2 analog on pig serum GH; and

FIG. **5** is a graph showing the effect of various doses of hGRF(1–29)NH_2 vs [Hexenoyl trans-3]^0 hGRF(1–29)NH_2 (TT-01024) on the GH area under the curve over 420 minutes following S.C. administration (**P<0.01 and ***P<0.001 when compared to the basal period—-60 to 0 min—).

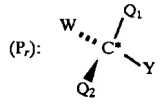
DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the use of fatty bodies, namely pseudomicellar residues and/or hydrophobic tails to produce a new family of highly potent, chimeric fatty body-pro-GRF analogs while remaining biodegradable and non immunogenic.

In accordance with the present invention, the fatty body-pro-GRF analogs can be chemically synthesized:

- by anchoring one or several hydrophobic tails at the C- and/or the N-terminal portion of GRF or one of its analogs, or
- by incorporating one or several pseudomicellar α amino acid derivative(s) ("pseudomicellar residue") in the chemical synthesis of GRF or one of its analogs.

In accordance with the present invention, the structure of pseudomicellar residues (P_r) used as a link in the synthesis of GRF and analogs thereof may be represented in the following manner:

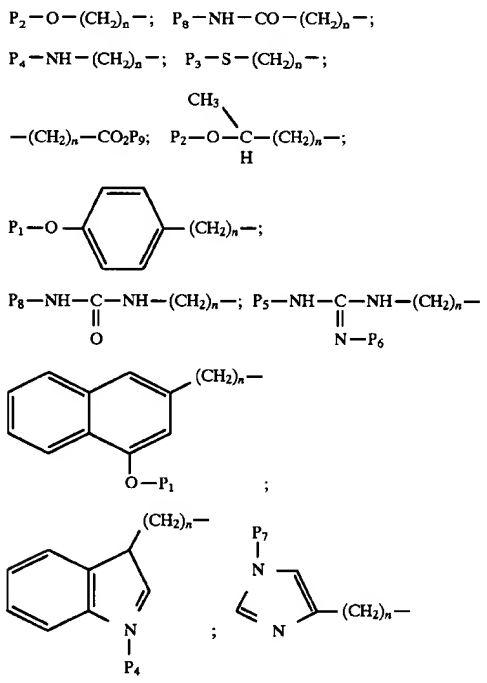


wherein:

W is a group selected from the group consisting of $—CO_2Q_3$; $—PO_3Q_3$ and $—SO_3Q_3$;

Q_3 is an hydrogen atom, an ammonium ion, an element selected from the group consisting the elements of group 1A of the Mendeléev periodical table, or a functional group derived from the following fatty bodies, pentenoic acids, hexenoic acids, heptenoic acids or their saturated forms;

Q_1 is a radical selected from the group consisting of alkenyl, aralkyl, aryl and alkyl ($C_{n1}H_{2n1+}1$), where n_1 is a number between 1 and 8. Q_1 may be selected from the following list, which is provided to illustrate the invention rather than to limit its scope:



wherein,

P_1 to P_9 represents a hydrogen atom; a methyl group; a functional hydrophobic tail with a main aliphatic, alicyclic or aromatic chain, linear or branched which may be selected from the following list: saturated fatty acid of general formula ($C_mH_{2m}O_2$) with m being a value between 4 and 12; or a lateral chain protecting group as described by Gross et Meienhofer (1981, *The peptides*, vol. 3, Academic press: pages 1–341) such that P_1 may be a benzyl group, bromo-2 benzyl, dichloro-2,6 benzyl or t-butyl; P2 may be a benzyl group or t-butyl; P_3 may be a benzyl group, t-butyl, trityl, acetamidomethyl or benzamidomethyl; P_4 may be trifluoroacetyl, t-butyloxycarbonyl (Boc), benzyloxycarbonyl (Z) or fluorenylmethyloxycarbonyl (Fmoc); P5 may be a nitro group, p-methoxybenzenesulfonyl, mesitylenesulfonyl, or pentamethylcromane; with the proviso that P_6 is hydrogen, or that P_5 and P_6 may be adamantyloxycarbonyl; P_7 may be a phenacyl group, benzyloxymethyl or t-butoxymethyl; P_8 may be a benzhydryl group, dimetoxybenzhydryl, trityl or xanthenyl;

n is an integer between 0 and 6;

Y is of the following general formula

wherein:

A is a bivalent heteroatom, preferably oxygen, sulfur, a —NH— group or a —N(Me)— group;

P_z is the same as P_1 to P_4 defined previously where Z is an integer between 1 to 4; and

Q_2 is an hydrogen atom. When Q_1=H or lower alkyl, Q_2 may be any alkyl, alcoxy, alkenyl, aralkyl, or aryl group. In these conditions it possesses the same chemical identity as defined above for Q_1.

The carbon atoms on which (Q_1) and (Q_2) are attached are of L or D configuration. They are asymmetrical but not when (Q_1)=(Q_2) or (W)=(Y).

In cases where the anchoring consists in one or more hydrophobic tails (Ht) non-pseudomicellar, the whole of the structure of said tails may be represented as follows:

wherein:

R is an alkyl, alkenyl, aryl or aralkyl radical of branched or linear chains, and may be derived from the group of metabolisable fatty bodies consisting of saturated fatty acids of the general formula $C_mH_{2m}O_2$, preferably with m being an integer between 4 and 6; mono or polyunsaturated fatty acids, fatty amines and alcohols;

X represent a phosphorous, a carbon or a sulfur atom;

f is an integer between 1 and 3;

Q_5 represent an hydrogen atom, an ammonium ion, or an alkaline metal ion; when f is an integer between 1 and 2, Q_5 may be defined as for R above with the proviso of having at least one of the following functions:

amino (—NH—); alcohol(—OH), thio (—SH), or acid ($—XO_fH$); with X and f being as defined above.

For a better carrying out of the chemical anchoring reaction, hydrophobic tails or pseudomicellar residues functionalized under the acid form are preferably used. In these conditions, the anchoring reaction is preferably effected in a solid phase (Merrifield R. B., 1963, *J. Am. Chem. Soc.*, 85:2149; 1964, *J. Am. Chem. Soc.*, 86:304) using extremely active reagents such as for example Benzotriazole-1-yloxytris (dimethylamino) phosphonium hexafluorophosphate known in the prior art (B. Castro et al., 1975, *Tetrahedron letters*, Vol. 14:1219).

The pseudomicellar residue to be anchored is generally prepared by the direct action of a malonic salt, preferably a sodium salt of diethylacetamidomethyl malonate, and the alkyl, alkenyl, aryl or aralkyl halide in a polar solvent such as dimethylformamide. This reaction is usually followed by an acid or alkaline hydrolysis and of a resolution (preferably enzymatic) of the resulting racemic mixture.

In certain conditions, the preparation of the pseudomicellar residue consists in:

a) a first step; to protect in an orthogonal fashion and to attached on a solid support of sasrin type (M. Mergler et al., 1988, *Peptides, Chemistry and Biology*, Proceedings of the 10th American peptide symposium, St. Louis, p.259, G. R. Marshall, Ed., Escom, leiden), an amino acid with a functionalized lateral chain such as lysine, glutamic acid or aspartic acid; and

b) a second step; to specifically deprotect the lateral chain and to anchor on the free site a metabolisable hydro-

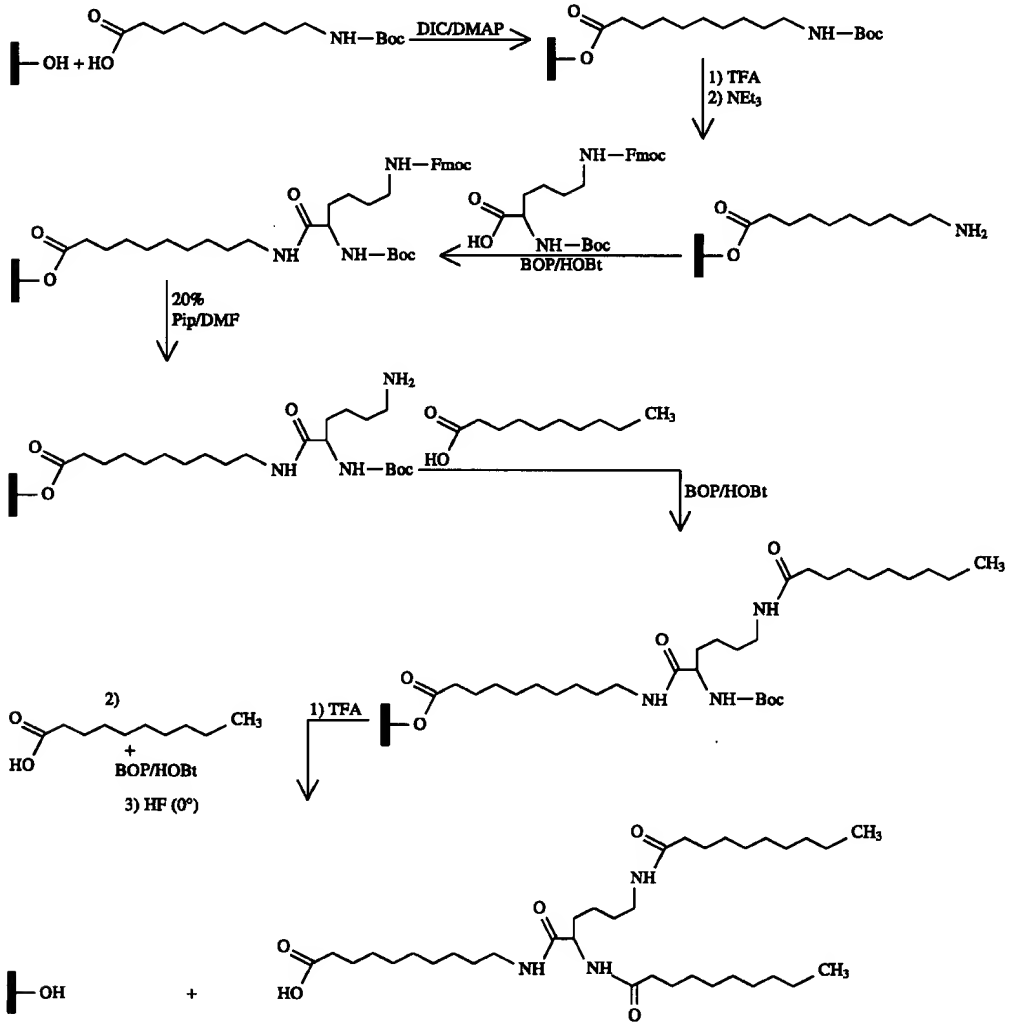
phobic tail (Ht) such as described above. The pseudomicellar residue (P_r) is thus obtained after a cleavage (0.5% TFA/CH_2Cl_2) of the support-residue bond, followed by purification steps.

The pseudomicellar residue may also be prepared by a selective complexion of the acid and the amine function in alpha of a trifunctional free amino acid, by complexing agents of mineral origin such as copper acetate. In these conditions, the anchoring of the metabolisable hydrophobic tail is effected by the direct action of the formed complex and of said tail, either in its acyl halide form or in its acid or amine form in the presence of a condensation agent.

In the case where the hydrophobic tail to be anchored consists in a fatty acid, the activation in view of the anchoring may be carried out in situ. Depending on the synthesis strategies used, the peptide anchoring site is liberated just prior to the anchoring in traditional deprotection conditions (Gross et Meienhofer, 1981, *The peptides*, vol. 3, Academic press: pages 1–341). The hydrophobic tail (Ht) or the pseudomicellar residue (P_r) is then condensed with the anchoring agent in organic solvents such as an ether (tetrahydrofuranne), an aliphatic halogenated solvent (dichloromethane), a nitrile (acetonitrile) or an amide (dimethylformamide).

With respect to the anchoring dynamic, the preferred working temperatures are between 20° and 60° C. The anchoring reaction time when hydrophobic tail used are more and more hydrophobic, varies inversely with temperature, but varies between 0.1 and 24 hours.

As an illustrative example, the triacyl lysine synthesis as set forth below illustrates in a schematic manner the whole of the anchoring principle of a hydrophobic fatty acid tail.



General GRF analogs synthesis steps were carried out by solid-phase methodology on a 9050™ plus peptide synthesizer (Millipore Corporation, Milford, Mass.) using Fmoc strategy and synthesis cycles supplied by Millipore. Fmoc amino acids were supplied by Bachem California and other commercials sources. Sequential Fmoc chemistry using BOP/HOBt as coupling methodology were applied to the starting Fmoc-Pal-PEG resin (Millipore, catalog number: GEN 913383) for the production of C-terminal carboxam-

ides. Fmoc deprotections were accomplished with piperidine 20% solution in DMF. After synthesis completion, the resin was well washed with DMF and ether prior to drying. Final cleavages of side chain protecting groups and peptide-resin bonds were performed using Millipore supplied procedure consisting of the following mixture: TFA, water, phenol, triisopropylsilane (88:5:5:2). Peptides were then precipitated and washed with ether prior to drying. Reverse phase HPLC purification (buffer A: TEAP 2.5; buffer B: 80% CH_3CN in A) using a water pep 4000, absorbance 214 nm, detector model 486, flow rate 50 ml/min.; linear gradient generally from 25 to 60% B in 105 min.) followed by a desalting step (buffer C:0.1% TFA in H_2O; buffer D:0.1% TFA in CH_3CH/H_2O 80:20) afforded peptides in yields amounting from 10 to 30% with homogeneity greater than 97% as estimated by HPLC (millennium/photodiode array detection).

In accordance with the present invention, pig was selected as a test specie, since it is a valuable preclinical model for the development of GRF analogs. Indeed, human and porcine GRF(1–29)NH_2 share a 100% homology of structure, and the physiological pattern of GH secretion is almost identical in both species.

Moreover, the potency of the GRF analogs was assessed as their ability to significantly increase IGF-I blood levels rather than their acute GH releasing potency. Indeed, it is known that the anabolic and healing effects of GH or GRF induced GH are mediated by an increase in IGF-I synthesis and secretion. Therefore, the measurement of GRF induced IGF-I elevation is the best indicator of the treatment efficacy.

The present invention will be more readily understood by referring to the following examples which are given to illustrate the invention rather than to limit its scope.

EXAMPLE I

EFFECT OF REPEATED ADMINISTRATIONS OF [BUTYRYL^0], [OCTANOYL^0]-, [HEXANOYL^0]-[HEXANOYL^{30}], [HEXANOYL^{0,30}],HGRF(1–29)NH_2 AND [HEXANOYL^0] HGRF(1–44)NH_2 VS HGRF(1–29) NH_2 ON SERUM IGF-I LEVELS IN PIGS

The objective of these experiments was to assess the potential of the GRF analogs as anabolic agents. It is known that GH or GRF-induced GH secretion exert their anabolic effect via an increase in insulin-like growth factor I (IGF-I) synthesis and secretion, that result in elevated levels of circulating IGF-I. It has been previously demonstrated that the intensity of the anabolic response to a GRF analog treatment is proportional to the increase in IGF-I levels in pigs (Dubreuil P. et al., 1990, *J. Anim. Sci.*, 68:1254–1268).

Therefore, in order to investigate the anabolic potency of the fatty acid-pro-GRF analogs, their ability to increase IGF-I levels following repeated S.C. administrations in pig was evaluated.

Experiment 1

26 LandracexYorkshire castrated male pigs (40–45 kg BW) were randomly distributed into 4 experimental groups:

1—hGRF(1–29)NH_2 (20 μg/kg, n=7)

2—[octanoyl^0] hGRF(1–29)NH_2 (20 μg/kg, n=6)

3—[hexanoyl^0] hGRF(1–29)NH_2 (20 μg/kg, n=6)

4—[butyryl^0] hGRF(1–29)NH_2 (20 μg/kg, n=7)

Each animal was injected BID (twice a day) subcutaneously for 4 consecutive days. One blood sample was collected each morning prior to the first injection of the day, and the day after the last injection, for IGF-I measurement.

Experiment 2

40 LandracexYorkshire castrated male pigs (40–45 kg BW) were randomly distributed into 5 experimental groups:

1—saline (n=8)

2—hGRF(1–29)NH_2 (40 μg/kg, n=8)

3—[hexanoyl^0] hGRF(1–29)NH_2 (10 μg/kg, n=8)

4—[hexanoyl^0] hGRF(1–29)NH_2 (20 μg/kg, n=8)

5—[hexanoyl^0] hGRF(1–29)NH_2 (40 μg/kg, n=8)

Each animal was injected BID (twice a day) subcutaneously for 5 consecutive days. One blood sample was collected each morning prior to the first injection of the day, and the day after the last injection, for IGF-I measurement.

Experiment 3:

48 LandracexYorkshire castrated male pigs (40–45 kg BW) were randomly distributed into 6 experimental groups:

1—Saline (n=8)

2—hGRF(1–44)NH_2 (30 μg/kg, n=8)

3—[hexanoyl^0]hGRF(1–44)NH_2 (30 μg/kg, n=8)

4—[hexanoyl^0]hGRF(1–29)NH_2 (20 μg/kg, n=8)

5—[hexanoyl^0]hGRF(1–29)NH_2 (20 μg/kg, n=8)

6—[hexanoyl^{0,30}]hGRF(1–29)NH_2 (20 μg/kg, n=8)

The selected doses were 30 μg/kg for hGRF(1–44)NH_2 analogs and 20 μg/kg for hGRF(1–29)NH_2 analogs, which give identical doses on a molar basis. Each animal was injected BID (twice a day) subcutaneously for 5 consecutive days. One blood sample was collected each morning prior to the first injection of the day, and the day after the last injection, for IGF-I measurements.

IGF-I measurements

IGF-I levels were measured in pig serum by double antibody radioimmunoassay after formic acid-acetone extraction, as previously described (Abribat T. et al., 1993, J. Endocrinol., 39:583–589). The extraction prior to radioimmunoassay is a necessary step to remove endogenous IGF-binding proteins.

Statistical analysis

In both experiments, the IGF-I data were analyzed by a two way repeated measure analysis of variance, with day and treatment (GRF analog) as sources of variation. Multiple comparison procedures were there run (Student-Newman Keuls method). A $P<0.05$ was considered as statistically significant.

Results

Experiment 1

There were both a significant effect of day ($P=0.0004$) and a significant treatmentxday interaction ($P=0.011$), indicating that the increase in IGF-I levels was dependent on the analog tested (Table 1). Blood samples for IGF-I measurements were collected daily prior to the first injection of compounds. Data are shown as mean ±SEM of 6 to 7 values per group.

TABLE 1

Effect of repeated SC injection (20μg/kg BID × 4 days) of GRF analogs on serum IGF-I levels

Treatment (BID, 20μg/kg SC)	Day 1 (pretreatment) (ng/ml)	Day 2 (ng/ml)	Day 3 (ng/ml)	Day 4 (ng/ml)	Day 5 (ng/ml)
hGRF(1–29)NH_2	252 ± 28	235 ± 19	263 ± 16	258 ± 17	262 ± 24
[octanoyl^0]hGRF(1–29)NH_2	316 ± 22	287 ± 20	301 ± 37	301 ± 37	318 ± 39
[hexanoyl^0]hGRF(1–29)NH_2	248 ± 20	281 ± 28	299 ± 26	319 ± 22[a]	342 ± 21[a,b]
[butyrl^0]hGRF(1–29)NH_2	278 ± 20	281 ± 24	302 ± 26	289 ± 26	293 ± 23

Treatment P = 0.42
Day P = 0.0004
Treatment × Day P = 0.011
[a]P < 0.05 when compared to day 1
[b]P < 0.05 when compared to day 2

Multiple comparisons revealed that only [hexanoyl^0] hGRF(1–29)NH_2 elicited an increase in IGF-I levels, which was significant on days 4 (29%, P<0.05) and 5 (38%, P<0.05). Human GRF(1–29)NH_2 had no effect on IGF-I levels at the dose tested.

Experiment 2

There were both a significant effect of day (P<0.0001) and a significant treatment×day interaction (P<0.0001), indicating that the increase in IGF-I levels was dependent on the analog tested (Table 2). Blood samples for IGF-I measurements were collected daily prior to the first injection of the day. Data are shown as mean ±SEM of 8 values per group.

TABLE 2

Treatment BID, SC	Day 1 (pretreatment) (ng/ml)	Day 2 (ng/ml)	Day 3 (ng/ml)	Day 4 (ng/ml)	Day 5 (ng/ml)	Day 6 (ng/ml)
saline	282 ± 33	266 ± 33	281 ± 34	293 ± 30	287 ± 32	289 ± 33
hGRF(1–29)NH_2 (40 μg/kg)	244 ± 24	243 ± 16	267 ± 20	275 ± 27	267 ± 17	256 ± 15
[hexanoyl^0]hGRF (1–29)NH_2 (10μg/kg)	303 ± 31	327 ± 20	337 ± 25	338 ± 25	366 ± 37[a]	350 ± 34[a]
[hexanoyl^0]hGRF (1–29)NH_2 (20 μg/kg)	302 ± 38	341 ± 37	368 ± 43[a]	362 ± 40[a]	362 ± 45[a]	368 ± 57[a]
[hexanoyl^0]hGRF (1–29)NH_2 (40 μg/kg)	252 ± 35	275 ± 32	319 ± 31[a]	354 ± 41[a,b]	350 ± 34[a,b]	374 ± 33[a,b,c]

Treatment P = 0.23; Day P = 0.0001
Treatment × Day P = 0.0001
[a]P < 0.05 when compared to day 1
[b]P < 0.05 when compared to day 2
[c]P < 0.05 when compared to day 3

Multiple comparisons revealed that all three tested doses of [hexanoyl^0] hGRF(1–29)NH_2 increased IGF-I levels. At 10 μg/kg, IGF-I levels were significantly increased at days 5 and 6 (16 to 21%, P<0.05). At 20 μg/kg, they were increased at days 3, 4, 5 and 6 (20 to 22%, P<0.05). At 40 μg/kg, they were increased at days 3, 4, 5 and 6 (27 to 48%, P<0.05). The serum IGF-I levels remained stable in saline—and hGRF(1–29)NH_2—treated pigs.

Finally, a regression analysis revealed that the increase in IGF-I concentrations from day 1 to day 6 was dependent on the dose of [hexanoyl^0] hGRF(1–29)NH_2 (ΔIGF-I=11.9+(2.77 * dose); r=0.68, P<0.0001).

Experiment 3:

There were both a significant effect of day (P<0.0001) and a significant treatment×day interaction (P<0.0001), indicating that the increase in IGF-I levels was dependent on the analog tested (Table IV). Multiple comparison revealed that analogs with an hexanoyl function branched at the N-terminal region of GRF were highly potent:

[hexanoyl^0] hGRF(1–29)NH_2 significantly increased IGF-I levels on days 5 and 6 (by 28% and 31%, P<0.05)

[hexanoyl$^{0,\ 30}$] hGRF(1–29)NH_2 significantly increased IGF-I levels on days 4, 5 and 6 (by 32%, 35% and 43%, P<0.05)

[hexanoyl^0] hGRF(1–44)NH_2 significantly increased IGF-I levels on days 3, 4, 5 and 6 (by 41%, 54%, 50% and 61%, P<0.05)

As previously observed for hGRF(1–29)NH_2 (experiments 1 and 2), the full length hGRF(1–44)NH_2 had little or no effect on IGF-I levels (except for a significant effect on day 5, which was not sustained on day 6). Finally, the anchoring of an hexanoyl function at the C-terminal region of hGRF(1–29)NH_2 yielded an analog with increased potency when compared to hGRF(1–29)NH_2 (21% increased in IGF-I levels on day 6, P<0.05), but less potent than [hexanoyl^0]hGRF(1–29)NH_2.

Human GRF(1–29)NH_2 and hGRF(1–44)NH_2 were injected at 20 μg/kg and 30 μg/kg, respectively, in order to achieve equimolar concentrations. Data shown are mean ±SEM of 8 values per group.

TABLE 3

Effect of multiple SC injections of GRF analogs (BID × 5 days) on serum IGF-I levels in growing pigs

Treatment BID, SC	Day 1 (pretreatment) (ng/ml)	Day 2 (ng/ml)	Day 3 (ng/ml)	Day 4 (ng/ml)	Day 5 (ng/ml)	Day 6 (ng/ml)
saline	215 ± 21	215 ± 28	219 ± 25	226 ± 28	249 ± 30	234 ± 24
hGRF(1–44)NH_2 (30μg/kg)	245 ± 21	254 ± 22	285 ± 26	297 ± 28	303 ± 26[a]	296 ± 26
[hexanoyl^0]hGRF(1–29)NH_2 (20μg/kg)	272 ± 45	292 ± 52	292 ± 57	315 ± 57	347 ± 44[a,b,c]	356 ± 44[a,b,c]
[hexanoyl^{30}]hGRF(1–29)NH_2 (20μg/kg)	297 ± 30	270 ± 25	287 ± 24	278 ± 18	276 ± 20	327 ± 24[b]
[hexanoyl^{0,30}]hGRF(1–29)NH_2 (20μg/kg)	205 ± 24	212 ± 26	253 ± 33	271 ± 36[a,b]	277 ± 29[a,b]	294 ± 26[a,b]
[hexanoyl^0]hGRF(1–44)NH_2 (30μg/kg)	241 ± 30	290 ± 33	340 ± 41[a]	372 ± 40[a,b]	361 ± 46[a,b]	388 ± 49[a,b,c]

Treatment P = 0.16
Day P < 0.0001
Treatment × Day P < 0.0001
[a]P < 0.05 when compared to day 1
[b]P < 0.05 when compared to day 2
[c]P < 0.05 when compared to day 3

Conclusions

Neither hGRF(1–29)NH_2 nor hGRF(1–44)NH_2 at doses ranging from 20 to 40 μg/kg were able to modulate IGF-I levels. However, the anchoring of fatty acid rendered GRF more potent and yielded analogs with markedly improved activity on IGF-I secretion. The anchoring of fatty acids was efficient in improving the anabolic potency of both hGRF (1–29)NH_2 and hGRF(1–44)NH_2. From the above results, it is concluded that the ideal fatty acid to use is hexanoic acid or any C_6 fatty derivative, and that it should be preferably anchored at the N-terminal region of GRF to yield maximally potent analogs.

EXAMPLE II

Comparative effects of pro-GRF analogs on IGF-I levels in pigs

This was a 5-day treatment, twice a day S.C. administration of one single dose of each test article vs saline. This experiment was conducted to compare the efficacy of $(Aminohexanoyl)_0$ hGRF (1–29) NH_2, $(Hexylformiate)_0$ hGRF (1–29) NH_2, $(Hexenoyl\ trans\text{-}2)_0$ hGRF (1–29) NH_2, $(Hexenoyl\ trans\text{-}3)_0$ hGRF (1–29) NH_2 and $(Muconoyl)_0$ hGRF (1–29) NH_2 to that of $(Hexanoyl)_0$ hGRF (1–29) NH_2.

All tested compounds belong to the same family of GRF analogs: they are a combination of the natural GRF and natural fatty acids, designed to improve the activity of the molecule.

Identity of tested analogs:

		in saline
TT-01015	$(Hexanoyl)_0$ hGRF (1–29) NH_2	20 μg/kg
TT-01021	$(Aminohexanoyl)_0$ hGRF (1–29) NH_2	20 μg/kg
TT-01022	$(Hexylformiate)_0$ hGRF (1–29) NH_2	20 μg/kg
TT-01023	$(Hexenoyl\ trans\text{-}2)_0$ hGRF (1–29) NH_2	20 μg/kg
TT-01024	$(Hexenoyl\ trans\text{-}3)_0$ hGRF (1–29) NH_2	20 μg/kg
TT-01025	$(Muconoyl)_0$ hGRF (1–29) NH_2	20 μg/kg

Route and frequency of test article

ADMINISTRATION: Two daily subcutaneous injections.

TEST SYSTEM: LandracexYorkshire pigs.

ANIMAL DESCRIPTION: Fifty six (56) growing barrows pigs weighing 35 kg at the time of purchase.

RATION: Commercial feed concentrate (18% protein) offered ad libitum.

EXPERIMENTAL DESIGN: Fifty six (56) pigs were randomly distributed into 7 experimental groups (n=8 pigs per group). Each group received two daily S.C. administration of the following treatments (volume: 3 ml, S.C. injection).

group 1: saline 2×/day
group 2: TT-01015 20 μg/kg 2×/day
group 3: TT-01021 20 μg/kg 2×/day
group 4: TT-01022 20 μg/kg 2×/day
group 5: TT-01023 20 μg/kg 2×/day
group 6: TT-01024 20 μg/kg 2×/day
group 7: TT-01025 20 μg/kg 2×/day

Treatments were administered from day 1 to 5. Immediately before the injections, one blood sample were collected from each animal, and additional blood samples were collected on day 6.

Blood samples were allowed to clot, serum was harvested by centrifugation and submitted to IGF-I assays.

Results are shown in FIG. 1 as D-IGF-I, which is defined as the increase in IGF-I levels from day 1 (pretreatment levels) to day 6 (after 5 days of GRFs administrations). Among all analog tested, only hexanoyl-, hexylformiate-, hexenoyl trans2- and hexenoyl trans3-hGRF(1–29)NH_2 significantly increased IGF-I levels over the 6-day study period, whereas aminohexanoyl and muconoyl-hGRF(1–29) NH_2 did not. Since hGRF(1–29)NH_2 has been shown to be ineffective at the same dose in the same conditions in previous assays (see Example I), these results show that the addition of various C6 carbon chains at the N-terminus region of GRF increases its bioactivity.

EXAMPLE III

Intravenous GH-releasing potency of $(Hexenoyl\ trans\text{-}3)_0$ hGRF (1–29) NH_2 vs hGRF(1–29)NH_2 in pigs

This experiment was conducted to test the I.V. acute GH-releasing potency of $(Hexenoyl\ trans\text{-}3)_0$ hGRF (1–29) NH_2, a pro-GRF analog, in a model physiologically close to human and to compare it to that of hGRF(1–29)NH_2.

$(Hexenoyl\ trans\text{-}3)_0$ hGRF (1–29) NH_2 is a combination of the natural hGRF(1–29)NH_2 and natural fatty acids. This study was a multidose, single I.V. injection study.

Identity of tested analogs:

TT-01024	(Hexenoyl trans-3)$_0$ hGRF (1–29) NH_2	0.25 μg/kg
TT-01024	(Hexenoyl trans-3)$_0$ hGRF (1–29) NH_2	1 μg/kg
TT-01024	(Hexenoyl trans-3)$_0$ hGRF (1–29) NH_2	4 μg/kg
hGRF(1–29)NH_2		0.25 μg/kg
hGRF(1–29)NH_2		1 μg/kg
hGRF(1–29)NH_2		4 μg/kg

Route and frequency of test article

ADMINISTRATION: intravenous acute injection.

TEST SYSTEM: LandracexYorkshire pigs.

ANIMAL DESCRIPTION: Fifty six (56) growing barrows pigs weighing 35 kg at the time of purchase.

RATION: Commercial feed concentrate (18% protein) offered ad libitum.

EXPERIMENTAL DESIGN: Fifty (56) pigs (4 spare animals) were cannulated (a catheter surgically implanted in one jugular vein) within on week, before the study. On days 1 and 7, cannulated animals were randomly distributed into 7 groups (n=4 pigs per group).

group 1: saline	
group 2: TT-01024	0.25 μg/kg
group 3: TT-01024	1 μg/kg
group 4: TT-01024	4 μg/kg
group 5: hGRF(1–29)NH_2	0.25 μg/kg
group 6: hGRF(1–29)NH_2	1 μg/kg
group 7: hGRF(1–29)NH_2	4 μg/kg

Blood samples for pGH assay were collected every 20 min from 1 hour before to 5 hours after GRF injections, with additional samplings 10 and 30 min after injection (n=21 samples). Blood samples are allowed to clot at +4° C. Serum will be harvested by centrifugation, stored at −20° C. and submitted to pGH assays.

Results are illustrated in FIGS. **2** and **3**. As shown in FIG. **2**, hGRF(1–29)NH_2 (4 μg/kg) induced a rapid GH release that was sustained for approximately 60 minutes following injection. In contrast, hexenoyl trans3-hGRF(1–29)NH_2 injected at the same dose increased GH levels over a longer period, approximately 260 minutes. In addition, the GH response in the first 60 minutes was moderate, suggesting that this analog acts as a pro-GRF, being processed in serum into native GRF in the minutes or hours following injection. As shown in FIG. **3**, which presents the effects of various doses of GRF and the analog on the GH area under the curve (0 to 300 minutes following injection), hGRF(1–29)NH_2 produced a significant effect on GH secretion at 4 μg/kg, but not at 0.25 or 1 μg/kg, whereas hexenoyl trans3-hGRF (1–29)NH_2 elicited a significant response at all 3 doses tested. In conclusion, these results show that hexenoyl trans3-hGRF(1–29)NH_2 is a GRF analog with increased potency on GH secretion, and suggest that it may act as a pro-GRF, being protected from enzymatic degradation in serum.

EXAMPLE IV

Subcutaneous GH-releasing potency of (Hexenoyl trans-3)$_0$ hGRF (1–29) NH_2 vs hGRF(1–29)NH_2 in pigs

This experiment was conducted to test the S.C. acute GH-releasing potency of (Hexenoyl trans-3)$_0$ hGRF (1–29) NH_2, a pro-GRF analog, in a model physiologically close to human and to compare it to that of hGRF(1–29)NH_2.

Identity of tested analogs:

TT-01024	(Hexenoyl trans-3)$_0$ hGRF (1–29) NH_2	0.31 μg/kg
TT-01024	(Hexenoyl trans-3)$_0$ hGRF (1–29) NH_2	1.25 μg/kg
TT-01024	(Hexenoyl trans-3)$_0$ hGRF (1–29) NH_2	5 μg/kg
TT-01024	(Hexenoyl trans-3)$_0$ hGRF (1–29) NH_2	20 μg/kg
hGRF(1–29)NH_2		1.25 μg/kg
hGRF(1–29)NH_2		5 μg/kg
hGRF(1–29)NH_2		20 μg/kg

Route and frequency of test article

ADMINISTRATION: Subcutaneous acute injection.

TEST SYSTEM: LandracexYorkshire pigs.

ANIMAL DESCRIPTION: Sixty four (64) growing barrows pigs weighing 35 kg at the time of purchase.

RATION: Commercial feed concentrate (18% protein) offered ad libitum.

EXPERIMENTAL DESIGN: Thirty six (36) pigs (4 spare animals) were cannulated (a catheter surgically implanted in one jugular vein) within one week, before the study. On days 1 and 7, cannulated animals were randomly distributed into 8 groups (n=4 pigs per group).

group 1: saline	
group 2: TT-01024	0.31 μg/kg
group 3: TT-01024	1.25 μg/kg
group 4: TT-01024	5 μg/kg
group 5: TT-01024	20 μg/kg
group 6: hGRF(1–29)NH_2	1.25 μg/kg
group 7: hGRF(1–29)NH_2	5 μg/kg
group 8: hGRF(1–29)NH_2	20 μg/kg

Blood samples for pGH assay were collected every 20 min from 1 hour before to 7 hours after GRF injections, (n=25 samples). Blood samples were allowed to clot at +4 CC. Serum is harvested by centrifugation, stored at −20° C. and submitted to pGH assays.

Results are shown in FIGS. **4** and **5**. As shown in FIG. **4**, the subcutaneous injection of 5 μg/kg hGRF(1–29)NH_2 induced a GH response in the first 60 minutes following administration, whereas the same injection of hexenoyl trans3-hGRF(1–29)NH_2 induced a GH response that was sustained for 240 minutes. The FIG. **5** illustrates the effect of various doses of the GRFs tested on the GH area under the curve over the study period, i.e. from 0 to 420 minutes following injection. Over this period, hGRF(1–29)NH_2 did not induce any significant GH response at any of the tested doses, whereas hexenoyl trans3-hGRF(1–29)NH_2 elicited significant increases of the GH AUC at 5 and 20 μg/kg. Altogether, these results suggest that hexenoyl trans3-hGRF (1–29)NH_2 is a highly potent GH secretagogue, even when subcutaneously administered.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i i i) NUMBER OF SEQUENCES: 2

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: peptide

(i i i) HYPOTHETICAL: NO

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Tyr Ala Asp Ala Ile Phe Thr Asn Ser Tyr Arg Lys Val Leu Gly Gln
1 5 10 15

Leu Ser Ala Arg Lys Leu Leu Gln Asp Ile Met Ser Arg Gln Gln Gly
20 25 30

Glu Ser Asn Gln Glu Arg Gly Ala Arg Ala Arg Leu
35 40

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: peptide

(i i i) HYPOTHETICAL: NO

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Tyr Ala Asp Ala Ile Phe Thr Asn Ser Tyr Arg Lys Val Leu Gly Gln
1 5 10 15

Leu Ser Ala Arg Lys Leu Leu Gln Asp Ile Met Ser Arg
20 25

We claim:

1. A chimeric fatty bodyGRF analog with increased biological potency, of the following general formula:

A1-A2-Asp-Ala-Ile-Phe-Thr-A8-Ser-Tyr-Arg-Lys-Val-Leu-A15-Gln-Leu-A18-Ala-Arg-Lys-Leu-Leu-A24-Asp-Ile-A27-A28-Arg-A30-R_o

wherein,

A1 is Tyr or His;

A2 is Val or Ala;

A8 is Asn or Ser;

A18 is Ser or Thr

A15 is Ala or Gly;

A24 is Gln or His;

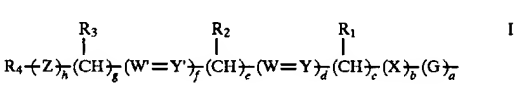
A27 is Met, Ile or Nle;

A28 is Ser or Asp;

A30 is any amino acid sequence of 1 to 15 residues;

R_o is NH2;

wherein A1 is N-anchored by a hydrophobic tail of the following general formula I:



I

wherein,

G is a carbonyl group;

X is a oxygen atom, sulfur atom or an amino group (NH);

(W=Y) represents cis or trans (CH=CR5);

(W'=Y') represents cis or trans (CH=CR6);

Z is an oxygen or a sulfur atom;

R_1, R_2 and R_3, independently, are selected from a hydrogen atom, and a linear or branched C_1–C_6 alkyl group;

R_4 is a hydrogen atom;

R_5 and R^6, independently, are a hydrogen atom or a linear or branched C_1–C_4 alkyl group;

a is 1;

b is 0;

c is 0 to 3;

d is 0 or 1;

e is 0 to 3;

f is 0 or 1;

g is 0 to 4;

h is 0 to 1;

wherein the sum of d+f=1 or 2 and the sum of a, b, c, d, e, f, g and h is such that the hydrophobic tail of formula I has a linear main chain of between 5 and 7 carbon atoms.

2. The chimeric fatty bodyGRF analog of claim **1**, wherein c is 0.

3. The chimeric fatty bodyGRF analog of claim **2**, wherein A30 is Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu.

4. The chimeric fatty bodyGRF analog of claim **3**, wherein R_0 is NH_2.

5. The chimeric fatty bodyGRF analog of claim **4**, of the formula cisCH_3—CH_2—CH=CH—CH_2—CO-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Rsn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu-NH_2 or transCH_3—CH_2—CH=CH—CH_2—CO-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-Gln-Gln-Gly-Glu-Ser-AsH-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu-NH_2.

6. The chimeric fatty bodyGRF analog of claim **1**, wherein the sum d+f=2; R_1, R_2, R_3 and R_4=hydrogen atom and the sum c+e+g=2, 3 or 4.

7. The chimeric fatty bodyGRF analog of claim **1**, wherein R_1, R_2, R_3 and R_4=hydrogen atom; and the sum c+e+g=3, 4 or 5.

8. The chimeric fatty body GRF analog of claim **4**, of the formula transCH_3—CH_2—CH=CH—CH_2—CO-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu-NH_2.

9. A pharmaceutical formulation for inducing growth hormone release which comprises as an active ingredient a GRF analog as claimed in claims **1** or **8**, in association with a pharmaceutically acceptable carrier, excipient or diluent.

10. A method of increasing the level of growth hormone in a patient which comprises administering to said patient an effective amount of a GRF analog as claimed in claims **1** or **8**.

11. A method for the diagnosis of growth hormone deficiencies in patients, which comprises administering to said patient a GRF analog as claimed in claims **1** or **8** and measuring the growth hormone response.

12. A method for the treatment of pituitary dwarfism or growth retardation in a patient, which comprises administering to said patient an effective amount of a GRF analog as claimed in claims **1** or **8**.

13. A method for the treatment of wound or bone healing in a patient, which comprises administering to said patient an effective amount of a GRF analog as claimed in claims **1** or **8**.

14. A method for the treatment of osteoporosis in a patient, which comprises administering to said patient an effective amount of a GRF analog as claimed in claims **1** or **8**.

15. A method for improving protein anabolism in human or animal, which comprises administering to said human or animal an effective amount of a GRF analog as claimed in claims **1** or **8**.

16. A method for inducing a lipolytic effect in human or animal inflicted with clinical obesity, which comprises administering to said human or animal an effective amount of a GRF analog as claimed in claims **1** or **8**.

17. A method for the overall upgrading of somatroph function in human or animal, which comprises administering to said human or animal an effective amount of a GRF analog as claimed in claims **1** or **8**.

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Attorney Docket No. 1736/44160

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

Michael IBEA et al.

Serial No.: 08/702,114 Group Art Unit: 1811

Filed: August 23, 1996 Examiner: Anish Gupta

For: CHIMERIC FATTY BODY-PRO-GRF ANALOGS WITH INCREASED BIOLOGICAL POTENCY

TERMINAL DISCLAIMER UNDER 37 C.F.R. §1.321

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

Theratechnologies Inc. of Montreal, Quebec, Canada, represents that it is the Assignee of the entire right, title and interest in above-captioned patent application by virtue of an assignment from the inventors recorded in the U.S. Patent and Trademark Office on microfilm reel 8227, at frame 0671; that the undersigned, whose title is supplied below, is empowered to act in its behalf, and that to the best of the undersigned's knowledge and belief title is in Theratechnologies Inc., and Theratechnologies Inc. hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the above-captioned application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. SS 154 to 156 and 173, of any patent granted on co-pending U.S. Patent Application Serial No. 08/702,113, filed August 23, 1996, and agrees that any patent granted on the above-captioned patent application shall be enforceable only for and during such period that the legal title to such patent shall be the same as the legal title to any patent granted on said co-pending U.S. Patent Application, this agreement to run with any patent granted on the above-captioned patent application and to be binding upon the grantee, its successors or assigns.

In making the above disclaimer, Theratechnologies Inc. does not disclaim the terminal part of any patent granted on the above-captioned application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. §§ 154 to 156 and 173 of any patent granted on said co-pending patent application in the event that it later expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. §1.321, has all claims cancelled by reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term.

A check in the amount of one hundred ten dollars ($110.00) is submitted herewith in payment of the required disclaimer fee under 37 C.F.R. §1.20(d). This amount is believed correct, however, the Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, to deposit account no. 05-1323 (Ref. Docket No. 1736/44160).

The undersigned hereby declares that all statements made herein of his own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

THERATECHNOLOGIES INC.

March 25, 1998
(date)

Jacques M. Saint-Denis
Vice President, Corporate Affairs

F

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,861,379
APPLICATION NO. : 08/702114
DATED : January 19, 1999
INVENTOR(S) : Michel Ibea, Thierry Abribat and Paul Brazeau

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 1, col. 21, line 59: delete "Thr" and substitute "Thr;"

Claim 1, col. 21, line 65: delete "NH2" and substitute "NH_2"

Claim 1, col. 22, line 54: delete "CR5" and substitute "CR_5"

Claim 1, col. 22, line 55: delete "CR6" and substitute "CR_6"

Claim 1, col. 22, line 60: delete "R^6" and substitute "R_6"

Claim 5, line 16: delete "Rsn" and substitute "Asn"

Claim 5, line 22: delete "AsH" and substitute "Asn"

Signed and Sealed this

Sixth Day of July, 2010

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
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Customer No 9486 | ISTMT | DATE PRINTED 05/14/2010

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FRANCE

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,861,379	**$440.00**	**$0.00**	**07/01/02**	**08/702,114**	**01/19/99**	**08/23/96**	**04**	**YES**	**1912-0151P**

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PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,861,379	**$1,150.00**	**$0.00**	**06/28/06**	**08/702,114**	**01/19/99**	**08/23/96**	**08**	**YES**	**1912-0151P**

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PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,861,379	**$2,055.00**	**$0.00**	**06/04/10**	**08/702,114**	**01/19/99**	**08/23/96**	**12**	**NO**	**I13724/C3**

PharmaResearch Corporation
4000 Aerial Center Parkway
Morrisville, North Carolina 27560
phone: 919.465.6000
fax: 919.469.4510
www.pharmaresearch.com

October 15, 2001

David Orloff, MD, Director
Division of Division of Metabolic and Endocrine Drug Products (HFD - 510)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Attention: Dr. Robert Perlstein

SUBJECT: TH9507
HUMAN GROWTH RELEASING FACTOR ANALOG
INVESTIGATIONAL NEW DRUG APPLICATION
SERIAL NO. 000

Dear Dr. Orloff:

On behalf of Theratechnologies, Inc. (Montreal, Quebec, Canada) and with reference to CFR 312.52, PharmaResearch Corporation, in its delegated role as the sole authorized US regulatory representative for Theratechnologies, Inc. (see Attachment A), herewith submits an Investigational New Drug Application for TH9507 [N-(trans-3-Hexenoly)-Human Growth Hormone Releasing Factor (1-44) Acetate], a growth hormone releasing factor analogue.

Reference is made to a Pre-IND meeting at FDA on July 20, 2000 attended by (FDA personnel) Drs. J. Jenkins, S. Malozowski, R. Perlstein, R. Anthracite, S. Moore, C.-H. Niu, J. El-Hage, J Wei, C. King, and Mr. D. Hertig. Theratechnologies representatives were Drs. N. Molfino and L. Lariviere, and Mr. J. Musto. The minute of this meeting (received on August 20, 2000) are enclosed (Attachment B).

Theratechnologies, Inc. is planning studies to evaluate the safety and efficacy of TH9507 for the initial indications of: (a) improved peripheral skeletal muscle functions in COPD and (b) shortening of recovery phase in prolonged immobilization. The protocol filed with this IND is designed in response to guidance and suggestions from the Agency in the July 20, 2000 meeting, and an early draft/synopsis was discussed by telephone with Dr. R. Perlstein and Dr. C. King on August 8, 2001.

During the meeting on July 20, 2000, FDA requested that Theratechnologies provide a review of relevant literature for IGF-1 and cancer risk. This literature review is included in the IND in Vol 16 section 10.1.

PharmaResearch

PharmaResearch Corporation
4000 Aerial Center Parkway
Morrisville, North Carolina 27560
phone: 919.465.6000
fax: 919.469.4510
www.pharmaresearch.com

During the meeting on July 20, 2000, FDA requested that Theratechnologies provide information on age- and sex-adjusted normative data for IGF-1 levels. These data are included in the IND in Vol 16 ,section 10.2.

The IND comprises 16 volumes, containing administrative information, the Investigator's Brochure, the protocol for study TH9507/II/DIABETIC/006, and the supporting CMC, virology, pharmacology and toxicology data. Three complete copies of the IND are provided.

Should you have any comments or questions regarding this submission, please do not hesitate to contact me at (919) 465-6006.

Sincerely Yours,

W. James Alexander, MD, MPH, FACP
Chief Medical and Regulatory Officer
PharmaResearch Corporation

cc: E. Borenstein, Theratechnologies, Inc.
A. Lefebvre, Theratechnologies, Inc.

I

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 61,226

PharmaResearch Corporation
US Agent for Theratechnologies, Inc.
Attention: W. James Alexander, MD, MPH, FACP
4000 Aerial Center Parkway
Morrisville, NC 27560

Dear Dr. Alexander:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 61,226

Sponsor: Theratechnologies, Inc.

Name of Drug: TH9507 for Injection

Date of Submission: October 15, 2001

Date of Receipt: October 16, 2001

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, on or before November 15, 2001, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will notify you immediately that (1) clinical studies may not be initiated under this IND ("clinical hold") or that (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have notified you that the information you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations).

Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, to the following address:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at 301-827-1090.

Sincerely,

{See appended electronic signature page}

Monika E. Johnson, Pharm. D.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Monika Johnson
10/24/01 03:09:30 PM

May 29, 2009

Original NDA
NDA No. 22-505
PROPRIETARY NAME: EGRIFTA™ (tesamorelin acetate for injection)

Mary Parks, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705

Dear Dr. Parks,

Theratechnologies, Inc. is submitting a new drug application (NDA No. 22-505) for EGRIFTA™ (tesamorelin acetate for injection) which is intended to be indicated to induce and maintain a reduction of excess abdominal fat in HIV-infected patients with lipodystrophy.
Kendle International has been designated the United States agent for this NDA.

Regulatory and Technical Point of Contact for the Application:

Michelle Wilson, Ph.D.
Senior Regulatory Consultant
Kendle International
Phone: 513.258.5766
Fax: 513.763.7628

EGRIFTA™ (tesamorelin acetate for injection) is a synthetic human Growth Hormone- Releasing Factor analogue that comprises the 44-amino acid sequence of human Growth Hormone-Releasing Factor (hGRF) with a binding affinity to hGRF receptors comparable to that of natural hGRF and an increased stability and half-life in humans. EGRIFTA™ is administered subcutaneously.

The efficacy of EGRIFTA™ in the treatment of excess abdominal fat in HIV-infected patients with lipodystrophy has been demonstrated in three pivotal studies (TH9507III/LIPO/010 and TH9507-CTR-1011, TH9507- CTR-1012). In studies TH9507III/LIPO/010 (main phase), and TH9507-CTR-1011, the primary efficacy endpoint was the percent change from baseline in visceral adipose tissue (VAT), as assessed by computed tomography (CT) scan, after 26 weeks of treatment with EGRIFTA™.

Theratechnologies Inc.
2310, boulevard Alfred-Nobel
Montreal (Quebec)
Canada H4S 2B4
Tél. / Phone: (514) 336-7800
Fax.: (514) 331-5082
www.theratech.com

Thera technologies

Treatment with daily doses of 2 mg EGRIFTA™ for 26 weeks in the pooled studies resulted in a significant decrease from baseline in VAT (13.1% in EGRIFTA™ -treated patients versus an increase of 2.3%inplacebo-treated patients). The primary endpoint results obtained during the first 26 weeks were sustained during the second 26 weeks of the trials with a change in VAT of 18% (studies TH9507III/LIPO/010 (extension phase) and TH9507-CTR-1012).

The secondary efficacy endpoints included improvements in lipids (triglycerides, total cholesterol to HDL-cholesterol ratio) and patient reported outcomes (PRO) related to body image, accompanied by an increase in insulin-like growth factor-I (IGF-I) level after 26 weeks of treatment. The main Patient Reported Outcome (PRO) endpoints, including belly appearance distress, belly size estimation and belly profile assessment, were measured using a validated PRO questionnaire, developed by Phase V Technologies, Inc., which analysed the results. All secondary endpoints supported the primary efficacy endpoint in the pooled studies.

The safety evaluation of EGRIFTA™ was established in 18 clinical studies including a total of 1,222 patients who received at least 1 dose of tesamorelin for a treatment period of up to 26 weeks. The results demonstrate that EGRIFTA™ was generally well tolerated.

Overall, there was no clinically significant difference between the tesamorelin and the placebo groups for mean change from baseline in FBG, insulin, HOMA-IR, and HbA1c.

The discontinuation rate was similar between EGRIFTA™- and placebo-treated patients. However, more EGRIFTA™-treated patients discontinued from clinical studies because of adverse events, which included those known to be related to the induction of GH secretion (including peripheral oedema, arthralgia, pain in extremity) as well as injection-site reactions.

The incidence of serious adverse events was comparable between patients treated with EGRIFTA™ and placebo.

Hypersensitivity reactions occurred in 3% of patients treated with EGRIFTA™. Patients with hypersensitivity reactions identified during the trials were discontinued as a precautionary measure.

In addition, in the pivotal trials, approximately half of the patients receiving EGRIFTA™ developed anti-tesamorelin IgG antibodies after 26 weeks of treatment. The prevalence of anti-tesamorelin IgG antibodies in patients treated for 52 weeks remained essentially unchanged from the first 26 weeks of treatment, at approximately 50%, through Week 52. The anti-tesamorelin IgG antibodies disappeared in a significant number of patients who switched to placebo for a 6 month period following 26 weeks of treatment with EGRIFTA™. In the eighteen percent (18%) of patients who still tested positive for anti-tesamorelin IgG antibodies at the end of the placebo treatment, the titers had decreased from the end of the EGRIFTA™ treatment period, suggesting that ceasing treatment results in seroreversion with time.

All patients treated with EGRIFTA™ for 52 weeks and positive for anti-tesamorelin IgG antibodies at Week 52 or early termination (the subject population potentially most at risk of developing neutralizing antibodies (NAbs)) were tested for both anti-hGRF and anti-tesamorelin NAbs. Five percent (5%) of these patients were found to be anti-hGRF NAb-positive; all of them had low titers (25). Overall, the presence of neutralizing hGRF antibodies had no impact on IGF-1 levels. Approximately ten percent of

patients treated with EGRIFTA™ for 52 weeks and positive for anti-tesamorelin IgG antibodies at Week 52 or early termination were found to be anti-tesamorelin NAb-positive. Overall, the presence of neutralizing tesamorelin antibodies had no impact on IGF-1 levels or VAT change from baseline or on the proportion of VAT responders. In addition, similar numbers of VAT responders were found between the anti-tesamorelin NAb-positive and anti-tesamorelin NAb-negative patients, indicating that the presence of anti-tesamorelin NAbs had no impact on efficacy.

Neutralizing activity against hGRF was measured in all samples collected at the last study visit/early termination (ET) visit from patients who switched from tesamorelin to placebo after 26 weeks of treatment (group T-P) and who were anti-tesamorelin IgG antibody-positive at Week 52 or ET. Three (3) out of 28 of these patients were anti-hGRF NAb positive. For those 3 patients, the IGF-1 level at time of discontinuation from the study was in the range of that observed in the overall subject population from the pivotal studies, suggesting that the presence of the anti-hGRF NAbs had no clinically significant impact on GH release.

In summary, the immunogenicity assessment of tesamorelin strongly suggests that the presence of anti-tesamorelin IgG antibodies, anti-hGRF and anti-tesamorelin NAbs has no impact on both the efficacy and safety of this product during tesamorelin treatment or after tesamorelin treatment is discontinued. With respect to long-term safety, the incidence of adverse drug reactions and serious adverse events among patients who received EGRIFTA™ over 52 weeks was similar to that among patients who received EGRIFTA™ over 26 weeks.

BRIEF REGULATORY HISTORY

A detailed summary of Sponsor-Agency communications and Agency meeting minutes are provided in Section 1.6.3: Correspondence.

NDA ORGANIZATION

This submission has been provided in electronic Common Technical Document (eCTD) format consistent with the FDA's *Final Guidance for Industry: Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (October 2005). The archival copy is a fully electronic dossier with the exception of administrative documents requiring an original signature, which are provided in paper.

Module 1	Regional Information
Module 2	Common Technical Document Summaries
2.2	Introduction
2.3	Quality Overall Summary
2.4	Nonclinical Overview

2.5	Clinical Overview
2.6	Nonclinical Written and Tabulated Summary
2.7	Clinical Summary
2.7.1	Summary of Biopharmaceutics and Analytical Methods
2.7.2	Summary of Clinical Pharmacology
2.7.3	Summary of Clinical Efficacy
2.7.4	Summary of Clinical Safety
Module 3	Quality
Module 4	Nonclinical
Module 5	Clinical

PEDIATRICS

Theratechnologies is requesting a waiver for studying the effects of tesamorelin in pre-pubertal children (see Section 1.9.1) and a deferral for conducting a study in post-pubertal children (see Section 1.9.2). As agreed during the pre-NDA meeting held on 19 September 2008 (see Section 1.6.3 Correspondence - FDA Meeting Minutes dated 14 October 2008), Theratechnologies will present its pediatric plan after the NDA is filed.

120 DAY SAFETY UPDATE

Theratechnologies will provide the following information in the 120 Day Safety Update:

1. Immunogenicity data:

   In addition to the substantial anti-tesamorelin and anti-hGRF neutralizing antibodies data already provided in the NDA, the 120 Day Safety Update will include the following additional supportive data:

   - For studies TH9507III/LIPO/010, TH9507-CTR-1011 and TH9507-CTR-1012 the following samples will be tested for anti-hGRF neutralizing antibodies:
     i. Last sample following 26 weeks of treatment for the group of patients that switched to placebo following 26 weeks of treatment with tesamorelin (T-P group)
     ii. Last sample following 52 weeks of treatment for the group of patients that switched to tesamorelin following 26 weeks of treatment with placebo (P-T group).

- The profiles of the following patients will be obtained:

  i. TH9507III/LIPO/010 (extension phase) and TH9507-CTR-1012 patients with positive anti-GRF NAbs screening at Week 26/52 (T-T, T-P, P-T) or early termination (T-T only). The T-T group is the group of patients treated with tesamorelin for 52 weeks
  ii. Patients with positive anti-hGRF NAbs screening at Week 26/52 (T-T, T-P, P-T) or early termination (T-T only)
  iii. TH9507III/LIPO/010(extension) and TH9507-CTR-1012 patients with positive anti-tesamorelin NAbs screening at Week 52 or ET (T-T group)

2. IgG results from follow-up visits for subjects positive for IgG at time of completion of study TH9507-CTR-1012 will be provided.

3. Updated safety information regarding the patients enrolled in ongoing studies conducted under Investigator INDs:

   • Dr. Steven Grinspoon
   - Protocol: Physiologic Effects of Long-Term GHRH 1-44 in Abdominal Obesity
   - Indication : Abdominal obesity
   - IND # 73329

   • Dr Michael V.Vitiello
   - Protocol title: Somatotrophics, Memory and Aging Research Trial (SMART Study)
   - Indication : GHRH : Cognition in aging and mild cognitive impairment
   - IND # : 67328

The 120 day safety update will be submitted on September 25th, 2009.

SUBMISSION INFORMATION: PDUFA FEE WAIVER

Please note that Theratechnologies has received a Small Business PDUFA Fee Waiver. The Size Determination Case is No.: 4-2009-32.

This submission is filed entirely in electronic Common Technical Document (eCTD) format; therefore, no Table of Contents is being provided. This eCTD has been generated by Octagon Research Solutions Inc., who has filed an acceptable eCTD pilot with the Center on June 2, 2004 (Pilot Number 900024). All electronic files included in this submission are provided on one DLT-IV 40/80 GB Tape and the electronic submission is approximately 19 Gb. All files were checked and verified to be free of viruses, prior to being written to DLT using Symantec Antivirus Corporate Edition, program version 8.1.0.825 and scan engine version 4.2.0.7 with a virus definition date of 5/27/2009 rev 3.

IT point of contact for this application

Gonçalo Coimbra, Assistant Director, Information Technology and Security
tel: 514 336-4804 ext. 280
email: gcoimbra@theratech.com)

Signature Page

Martine Ortega, PharmD
Vice president, Compliance and Regulatory Affairs
Theratechnologies Inc.

Michelle Wilson, PhD
US Agent/Contact for content related questions
Senior Regulatory Consultant
Kendle International

K

Date	Description	Serial No.
July 20, 2000	Pre-IND Meeting with the FDA	
October 15, 2001	IND submission to evaluate the safety and efficacy of TH9507. The protocol filed with the IND was designed in response to guidance and suggestions from the Agency in the July 20, 2000 meeting, and from an early draft/synopsis discussed by telephone with medical reviewers on August 8, 2001. The IND comprises 16 volumes containing administrative information, the Investigator's Brochure, the protocol for TH9507/II/DIABETIC/006 study, and supporting CMC, virology, pharmacology and toxicology data.	000
October 22, 2001	Submission of minutes from the Pre-IND meeting of July 20, 2000.	001
October 24, 2001	FDA letter acknowledging IND receipt on October 16, 2001 and providing IND Number 61,226.	
November 1, 2001	Submission of Changes in the sequencing data requested by CMC reviewers.	002
November 20, 2001	Submission of Changes to TH9507/II/DIABETIC/006 protocol (amendment 1).	003
December 12, 2001	Submission of Change in Drug Product manufacturer.	004
February 15, 2002	Submission of New Investigator information regarding TH9507/II/DIABETIC/006 study.	005
April 8, 2002	Submission of Changes to TH9507/II/DIABETIC/006 protocol (amendment 2).	006
May 21, 2002	Submission of New Investigator information regarding TH9507/II/DIABETIC/006 study.	007
May 31, 2002	Submission of Changes to TH9507/II/DIABETIC/006 protocol (amendment 3).	008
January 15, 2003	IND Annual Report 2002.	009
February 3, 2003	Submission of Pharmacology and Toxicology study reports.	011
February 4, 2003	Submission of Press Release in relation to TH9507/II/DIABETIC/006 study.	010

Date	Description	Serial No.
February 12, 2003	• Submission of Draft Synopsis of results for TH9507/II/DIABETIC/006 study. • Submission of Protocol Synopsis for TH9507/II/LIPO/008 study.	012
March 7, 2003	• Submission of Clinical Protocol for TH9507/II/LIPO/008 study. • Submission of New Investigator information regarding TH9507/II/LIPO/008 study.	013
April 30, 2003	Submission of a Letter authorizing an Investigator's IND to refer to IND number 61,226.	014
May 12, 2003	Submission of New Investigator information regarding TH9507/II/LIPO/008 study.	015
May 28, 2003	Submission of Canadian Press Release in relation to TH9507/II/LIPO/008 study.	016
June 20, 2003	Submission of Labeling and Manufacturer for assembly of clinical study supply kits for TH9507/II/LIPO/008 study.	017
July 1, 2003	• Submission of Changes in TH9507/II/LIPO/008 protocol (amendment 1). • Submission of New Investigator information regarding TH9507/II/LIPO/008 study.	018
July 23, 2003	Submission of Clinical Protocol for TH9507/II/SLEEP/005 study.	019
October 20, 2003	Submission of New Investigator information regarding TH9507/II/LIPO/008 study.	020
November 13, 2003	Submission of Cardiovascular Safety Pharmacology Final study report.	021
November 13, 2003	Submission of Revised Investigator's Brochure.	022
December 16, 2003	Submission of Canadian Press Release in relation to TH9507/II/LIPO/008 study.	023
January 13, 2004	IND Annual Report 2003.	024
April 15, 2004	Submission of Canadian Press Release in relation to TH9507/II/LIPO/008 study.	025
April 30, 2004	Submission of Change in Authorized representative.	026
August 12, 2004	Submission of Change in site for stability.	027

Date	Description	Serial No.
December 16, 2004	• Request for Type C Meeting to discuss proposed development of TH9507 for treatment of excess abdominal fat accumulation in HIV-associated lipodystrophic patients. • Submission of Draft Executive summary results for TH9507/II/LIPO/008 study. • Submission of Clinical protocol outline for TH9507/III/LIPO/010 study. • Submission of Revised Investigator's Brochure.	028
January 7, 2005	IND Annual Report 2004.	029
January 21, 2005	Submission of Information Package for Type C Meeting.	030
January 25, 2005	FDA letter to confirm Type C meeting.	
February 28, 2005	Submission of Safety report – Initial safety report: Preclinical Finding.	031
March 15, 2005	FDA request for information regarding Serial No. 031.	
March 24, 2005	FDA draft responses to questions addressed in Information Package Type C meeting.	
March 30, 2005	Type C meeting with the FDA.	
April 21, 2005	Request for Type C Meeting to discuss CMC information.	032
April 27, 2005	Submission of Type C Meeting draft minutes and Authorized representative changes.	033
April 27, 2005	FDA official minutes of Type C meeting held on March 30, 2005.	
May 4, 2005	FDA response to request for Type C meeting to discuss CMC information.	
May 20, 2005	• Submission of Clinical Protocol for TH9507/II/LIPO/010 study. • Submission of New Investigator information regarding TH9507/II/LIPO/010 study.	034
May 25, 2005	Submission of Safety report – Follow-up to a written report: Preclinical Finding (Serial no. 031).	035
June 7, 2005	Submission of CMC Information Package.	036
July 6, 2005	Submission of New Investigator information regarding TH9507/II/LIPO/010 study.	037

Date	Description	Serial No.
July 20, 2005	• Submission of Changes in TH9507/II/LIPO/010 protocol (amendment 1) • Submission of New Investigator information regarding TH9507/II/LIPO/010 study.	038
August 10, 2005	Submission of CMC Request for clarification.	039
August 25, 2005	FDA request for Embryo Fœtal Toxicity study at higher doses.	
September 2, 2005	• Submission of Changes in TH9507/II/LIPO/010 protocol (amendment 2). • Submission of New Investigator information regarding TH9507/II/LIPO/010 study.	040
September 7, 2005	• Submission of Safety Report – Follow-up to a written report: Preclinical Finding (Serial Nos+C101. 031 and 035) • Request for assessment on the Conduct of Carcinogenicity Studies.	041
September 12, 2005	• Request for Teleconference to discuss Teratology study. • Submission of Additional information for CMC clarification.	042
September 22, 2005	FDA response to request for clarification (Serial No. 039).	
October 12, 2005	Teleconference with the FDA for discussing CMC information and Teratology study.	
October 24, 2005	Submission of Minutes from teleconference discussing Teratology study.	043
November 17, 2005	• Submission of Changes in TH9507/II/LIPO/010 protocol (amendment 3). • Submission of New Investigator information regarding TH9507/II/LIPO/010 study.	044
December 20, 2005	FDA letter concurring that non-clinical carcinogenicity studies are not required for TH9507.	
December 21, 2005	IND Annual Report 2005.	045
January 24, 2006	Submission of New Investigator information regarding TH9507/II/LIPO/010 study.	046
January 25, 2006	Follow-up to Type C meeting and Proposal for PRO clinically Minimal Important Difference in relation to TH9507/II/LIPO/010 study.	047

Date	Description	Serial No.
March 2, 2006	• Submission of Safety Report - Initial safety report: TH9507/III/LIPO/010 finding. • Submission of Revised Investigator's Brochure.	048
March 3, 2006	• Submission of Changes in TH9507/II/LIPO/010 protocol (Amendment no. 4). • Submission of New Investigator information regarding TH9507/II/LIPO/010 study.	049
March 14, 2006	Submission of Safety report – Follow-up to a written report: TH9507/III/LIPO/010 finding (Serial No. 048).	050
March 24, 2006	FDA minutes of CMC teleconference held on Oct. 12, 2005.	
April 14, 2006	Submission of Study Report for TH9507/I/HV/002 study.	051
May 31, 2006	Submission of Safety Report - Initial written report TH9507/III/LIPO/010 Finding.	052
June 5, 2006	• Submission of New Investigator information regarding TH9507/II/LIPO/010 study. • Submission of Statistical analysis Plan for TH9507/III/LIPO/010.	053
June 14, 2006	Submission of Special Protocol Assessment for Clinical study TH9507-CTR-1011.	054
July 13, 2006	Submission of Safety report - Follow-up to a written report: TH9507/III/LIPO/010 Finding (Serial No. 052).	055
July 31, 2006	Submission of Safety report - Follow-up to a written report: TH9507/III/LIPO/010 Finding (Serial No. 055).	056
August 1, 2006	FDA response to Special Protocol Assessment for Clinical study TH9507-CTR-1011.	
August 17, 2006	Submission of New Safety Information related to immunogenicity findings for TH9507/III/LIPO/010 study.	057
September 13, 2006	• Submission of Revised Investigator's Brochure. • New safety information: Follow-up on the Information submitted on August 17, 2006 for TH9507/III/LIPO/010 study.	058
September 14, 2006	Submission of Safety Report - Initial safety report: TH9507/III/LIPO/010 Finding.	059

Date	Description	Serial No.
October 2, 2006	Submission of Safety report - Follow-up to written report: TH9507/III/LIPO/010 Finding (Serial Nos. 057 and 058).	060
October 19, 2006	FDA request for information regarding Serial No. 060.	
October 26, 2006	Submission in response to FDA letter dated October 19, 2006.	061
November 10, 2006	• Submission of Changes to TH9507-CTR-1011 protocol. • Submission of Changes to TH9507/III/LIPO/010 protocol. • Update on safety information.	062
November 16, 2006	• Submission of Safety Report - Follow-up to a written report: TH9507/III/LIPO/010 Finding (Serial No. 059). • Change in US Agent Contact.	063
February 6, 2007	Submission of Safety Report - Follow-up to written report: TH9507/III/LIPO/010 Finding (Serial Nos. 059 and 063).	064
February 6, 2007	IND Annual Report 2006.	065
February 9, 2007	Submission of New Investigator information regarding TH9507-CTR-1011 study.	066
February 9, 2007	Submission of Changes to TH9507-CTR-1011 protocol (amendment 2)	067
March 17, 2007	FDA comments and recommendations regarding information submitted under Serial No. 061.	
May 4, 2007	Submission of New Investigator information regarding TH9507-CTR-1011 study.	068
May 4, 2007	Submission of Safety Report - Follow-up to written report: TH9507/III/LIPO/010 Finding (Serial Nos. 059 and 063).	069
May 18, 2007	Submission of information related to FDA immunology review.	070
June 8, 2007	Submission of New Investigator information regarding TH9507-CTR-1011 study.	071
June 14, 2007	• Submission of New protocol for TH9507-CTR-1012 study. • Submission of Revised Investigator's Brochure.	072
July 10, 2007	FDA comments and recommendations regarding information submitted under Serial No. 070.	

Date	Description	Serial No.
July 17, 2007	Submission of Information: Rationale for the use of an analytical method for product potency assessment for lot release. Request for review and comment.	073
July 20, 2007	• Submission of Information related to Pharmacology/Toxicology. • Request for review and comment.	074
August 6, 2007	Submission of New Investigator information regarding TH9507-CTR-1011 study.	075
August 22, 2007	Submission of briefing document for September 10, 2007 FDA meeting.	076
September 19, 2007	FDA comments and recommendations regarding information submitted under Serial No. 070.	
September 21, 2007	Request for End of Phase 2 (EOP2) meeting with FDA	077
October 1, 2007	Submission of Changes to TH9507-CTR-1011 protocol (amendment 3).	078
October 3, 2007	Submission of Safety Report - Initial safety report: TH9507-CTR-1011 Finding.	079
October 17, 2007	Submission of Safety Report - Initial safety report: TH9507-CTR-1011 Finding.	080
October 26, 2007	Submission of Statistical analysis plans for the first 26 weeks (Attachments 1 & 2) and for the extension phase (Attachments 3 & 4) of the TH9507/III/LIPO/010 clinical study.	081
November 5, 2007	Submission of Safety Report - Initial safety report: TH9507-CTR-1011 Finding.	083
November 6, 2007	Submission of Changes to TH9507-CTR-1011 protocol (amendment 3).	082
November 7, 2007	FDA responses to CMC questions submitted under Serial No. 073.	
November 9, 2007	Submission of Briefing Document for End of Phase 2 (EOP2) meeting of December 3rd, 2007.	084
December 3, 2007	Submission of Final Report for the Pharmacology/Toxicology study.	085
December 3, 2007	End of Phase 2 (EOP2) meeting with the FDA.	

Date	Description	Serial No.
December 18, 2007	FDA minutes of End of Phase 2 (EOP2) meeting held on December 3, 2007.	
December 20, 2007	Submission of Safety Report - Initial safety report: TH9507-CTR-1011 Finding.	086
January 18, 2008	Submission of New Investigator information regarding TH-9507-CTR-1011 study.	087
January 25, 2008	Submission of New Investigator information regarding TH9507-CTR-1011 study.	088
February 7, 2008	Submission of New Investigator information regarding TH9507/III/LIPO/010 study.	089
February 8, 2008	Submission of Safety Report - Follow-up to a written report: TH9507-CTR-1011 Finding (Serial No. 079).	090
February 13, 2008	Submission of Safety report - Follow-up to written report TH9507-CTR-1011 Finding (Serial No. 086).	091
February 19, 2008	Submission of Safety Report - Initial safety report: TH9507-CTR-1011 Finding.	092
February 19, 2008	• Submission of Changes to TH9507-CTR-1012 protocol. • Submission of Revised Master Informed Consent. • IND Annual Report 2007.	093
February 27, 2008	Submission of Revised Investigator's Brochure.	094
March 7, 2008	Submission of New Investigator information regarding TH9507-CTR-1012 study.	095
March 11, 2008	Submission of New Investigator information regarding TH9507-CTR-1011 study.	096
March 12, 2008	Submission of Safety Report - Follow-up to a written report: TH9507-CTR-1011 Finding (Serial No. 092).	097
March 20, 2008	Submission of Changes to TH9507-CTR-1015 protocol and of an Informed Consent Form.	098
March 21, 2008	Submission of Safety Report - Second follow-up to a written report: TH9507-CTR-1011 Finding (Serial Nos. 092 and 097).	099
April 8, 2008	Submission of New protocols for TH-9507-CTR-1019 and TH9507-CTR-1020.	100

Date	Description	Serial No.
April 11, 2008	Submission of Statistical analysis plan for TH9507-CTR-1011 study.	101
April 28, 2008	Submission of Safety Report - Second follow-up to a written report: TH9507-CTR-1011 Finding (Serial Nos. 086 and 091).	102
May 1, 2008	Submission of Safety Report - Second follow-up to a written report: TH9507-CTR-1011 Finding (Serial Nos. 079 and 090).	103
May 8, 2008	Submission of New Investigator information regarding TH9507-CTR-1011 and TH9507-CTR-1012 studies.	104
May 14, 2008	Submission of Safety Report - Initial safety report: TH9507-CTR-1012 Finding.	105
May 21, 2008	Submission of Safety Report - Initial safety report: TH9507-CTR-1012 Finding.	106
May 28, 2008	Meeting request for a pre-NDA meeting in relation with Clinical matters and the proposed Labeling.	107
May 28, 2008	Meeting request for a pre-NDA meeting with the Division of Endocrine and Metabolic Drug Products in relation with CMC matters.	108
June 3, 2008	Submission of Safety Report - Initial safety report: TH9507-CTR-1012 Finding.	109
June 10, 2008	• Submission of a revised statistical analysis plan for the TH9507-CTR-1011 study. • Submission of a PRO Statistic Analytical Plan for the TH9507-CTR-1011.	110
June 12, 2008	Submission of Safety Report - Initial safety report: TH9507-CTR-1011 and TH9507-CTR-1012 Finding.	111
June 20, 2008	Submission of Safety report - Follow-up to a written report: TH9507-CTR-1011 and TH9507-CTR-1012 Finding (Serial No. 080).	112
July 2, 2008	FDA letter to confirm Pre-NDA meeting to be held on Sept. 19, 2008.	
July 3, 2008	Submission of information related to the definition of responder used in the PRO analysis.	113

Date	Description	Serial No.
July 8, 2008	Submission of information related to a change in study medical overview of ongoing studies.	114
July 15, 2008	Submission of Safety Report - Initial safety report: TH9507-CTR-1012 Finding.	115
July 18, 2008	Submission of Safety Report - Follow-up to a written report: TH9507-CTR-1011 Finding (Serial No. 083).	116
July 18, 2008	Submission of CMC Briefing Document.	117
August 6, 2008	Submission of Safety report - Follow-up to a written report: TH9507-CTR-1011 and TH9507-CTR-1012 Finding (Serial No. 111).	118
August 8, 2008	Submission of two Immunology Assay Validation Reports.	119
August 8, 2008	Submission of Pre-NDA Clinical Briefing Document	120
August 19, 2008	Submission of Immunology Assay Validation Report.	121
August 22, 2008	Submission of Four (4) clinical study reports : TH9507/II/SLEEP/002, TH9507/II/IR/007, TH9507/II/Diabetic/006, and TH9507/II/HF/004.	122
August 28, 2008	FDA responses to CMC questions submitted under Serial No. 117.	
September 4, 2008	Submission of Clinical Trial Report for TH9507/II/SLEEP/005 Phase 2.	123
September 9, 2008	Submission of Safety Report - Follow-up to a written report: TH9507-CTR-1012 Finding (Serial No. 109).	124
September 11, 2008	Submission of Clinical Study Report for TH9507/II/LIPO/008 study.	125
September 19, 2008	Pre-NDA meeting with the FDA	
October 9, 2008	Submission of Information related to Immunology Assays.	126
October 14, 2008	FDA minutes of Pre-NDA meeting held on September 19, 2008.	
October 22, 2008	Correction of dates on the written reports filed under Serial Nos. 111 and 118 related to TH9507-CTR-1011 and TH9507-CTR-1012 studies.	127

Date	Description	Serial No.
October 28, 2008	Submission of New Investigator information regarding TH9507-CTR-1012 and TH9507-CTR-1015 studies.	128
November 4, 2008	• Submission of Safety Report - Initial safety report: TH9507-CTR-1012 Finding. • Submission of Safety Report - Follow-up to a written report: TH9507-CTR-1011 and TH9507-CTR-1012 (Serial Nos. 111 and 118).	129
November 5, 2008	Submission of Statistical analysis plan (SAP) for the TH9507-CTR-1012 study.	130
November 10, 2008	Submission of Clinical Trial Report for TH9507/II/COPD/003 study.	131
November 10, 2008	• Submission of Safety Report - Follow up to a written report: TH9507-CTR-1011 and TH9507-CTR-1012 (Serial No. 0129). • Submission of Safety Report - Follow-up to a written report: TH9507-CTR-1012 (Serial No. 0115).	132
November 19, 2008	• Submission of Safety Report - Follow-up on a written report: TH9507-CTR-1012 Finding (Serial Nos. 115 and 132). • Submission of additional information related to TH9507-CTR-1011 study.	133
November 24, 2008	Submission of Statistical analysis plan (SAP) for the patient reported outcomes for study TH9507-CTR-1012.	134
November 24, 2008	• Submission of Safety Report - Follow-up on a written report: TH9507-CTR-1012 Finding (Serial Nos. 109 and 124). • Submission of Safety Report - Follow-up on a written report: TH9507-CTR-1011 and TH9507-CTR-1012 Finding (Serial No. 129).	135
January 23, 2009	• IND Annual Report 2008. • Submission of protocols for TH9507-CTR-1016 and TH9507-CTR-1017 studies.	136
January 23, 2009	Submission of New Investigator information regarding TH9507-CTR-1012 study.	137
January 28, 2009	Submission of New Investigator information regarding TH95-CTR-1012 study.	138
February 5, 2009	FDA responses to questions submitted under Serial No. 126.	

Date	Description	Serial No.
February 10, 2009	Submission of Clinical study reports for TH9507-CTR-1016 and TH9507-CTR-1017 studies.	139
February 20, 2009	Submission of Revised Investigator's Brochure.	140
February 20, 2009	Submission of Clinical study reports for TH9507/PKPD-009 and TH9507-CTR-1015 studies.	141
February 24, 2009	Submission of Changes in TH9507-CTR-1012 protocol.	142
February 26, 2009	Responses to FDA Immunology questions.	143
May 29, 2009	Submission of the NDA	

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

NDA 22-505

NDA ACKNOWLEDGMENT

Kendle International Inc.
Attention: Michelle Wilson, Ph.D.
Senior Regulatory Consultant
U.S. Agent for Theratechnologies Inc.
441 Vine Street, Suite 500
Cincinnati, OH 45202

Dear Dr. Wilson:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Egrifta (tesamorelin acetate) for Injection

Date of Application: May 29, 2009

Date of Receipt: May 29, 2009

Our Reference Number: NDA 22-505

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **July 28, 2009** in accordance with 21 CFR 314.101(a).

Please note that you are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 USC §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) control numbers. 42 USC 282(j)(5)(B). You did not include such certification when you submitted this application. You may use Form FDA 3674, *Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank*, to comply with the

certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trials referenced in this application. Additional information regarding the certification form is available at: http://internet-dev.fda.gov/cder/regulatory/FDAAA_certification.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information on registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jennifer Johnson
6/17/2009 11:42:17 AM

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,861,379
APPLICATION NO. : 08/702114
DATED : January 19, 1999
INVENTOR(S) : Michel Ibea, Thierry Abribat and Paul Brazeau

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 1, col. 21, line 59: delete "Thr" and substitute "Thr;"

Claim 1, col. 21, line 65: delete "NH2" and substitute "NH_2"

Claim 1, col. 22, line 54: delete "CR5" and substitute "CR_5"

Claim 1, col. 22, line 55: delete "CR6" and substitute "CR_6"

Claim 1, col. 22, line 60: delete "R^6" and substitute "R_6"

Claim 5, line 16: delete "Rsn" and substitute "Asn"

Claim 5, line 22: delete "AsH" and substitute "Asn"

Signed and Sealed this

Sixth Day of July, 2010

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,861,379
DATED : January 19, 1999

INVENTOR(S): Michel Ibea; Thierry Abribat; and Paul Brazeau

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Claim 5, line 22: delete "AsH" and substitute "Asn"

MAILING ADDRESS OF SENDER:
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Minneapolis, MN 55402-0903

PATENT NO. 5,861,379
Docket No. 16575.00000002
No. of add'l copies 0